

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

DDVP

Chemical Code # 187, Tolerance # 235
SB 950 # 16

January 21, 1987

Revised 10/27/87, 6/2/89, 11/07/89, 4/26/90, 7/5/90, 11/15/90, 07/11/91, 7/1/92, 12/11/92,
2/9/93, 9/2/93, 2/1/94, 2/10/95, 7/7/95, 12/12/95, 6/12/98, 6/17/99 and 11/9/99

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, possible adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, possible adverse effect
Neurotoxicity:	No data gap, possible adverse effect

Toxicology one-liners are attached.

All record numbers applicable to SB-950 through 137355 and 911218 were examined. This includes all reports indexed as of 7/7/95. Note: Revision of 6/12/98 contains a publication from the open literature with a possible adverse effect (Gee, 6/12/98).

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T991109

Revised by: Stanton Morris, 7/11/91; J. Gee, 7/1/92; C. Aldous, 12/11/92; J. Gee, 2/9/93; T. Moore, 9/2/93; T. Kellner, 2/1/94; M. Silva, 2/10/95 & 7/7/95; J. Gee, 6/12/98, 6/17/99, 11/9/99.

Note: these pages contain summaries only. Individual worksheets may identify additional effects.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

CHRONIC TOXICITY, RAT

NOTE: Although no single rodent study independently fills the "rodent chronic" study data gap, the collective data on rodent chronic effects from three major rodent studies (095:074933, 071:035425, and 050:088033) adequately address general chronic toxicity in the rat. All three of the above studies exposed rats to levels near to an MTD, yet none found non-neoplasia effects of concern in any target tissue. A recent dog study (106:088784) also tested a dosage range at or near practical limits of exposure. In all cases, upper limits on acceptable dose levels elicited symptoms consistent with cholinesterase enzyme toxicity. The rodent chronic study data gap is considered "filled", with no adverse effects" indicated for non-neoplasia effects. Aldous, 11/14/90.

235-070 035423 "The Effects Exerted upon Rats during a Period of Two Years by the Introduction of Vapona Insecticide into their Daily Diets" (Kettering Lab, 2/14/67). DDVP (dichlorvos, Vapona), 93% initially by weight. 40/sex/group were fed at 0, 0.1, 1, 10, 100 or 500 ppm nominal; 22-80% loss of test article due to volatilization and hydrolysis in feed, which was mixed weekly. Interim sacrifices at 26, 52 and 78 weeks of 5/sex/group with 25/sex/group scheduled to be fed to term. ChE NOEL = 10 ppm nominal (blood cholinesterase inhibition), systemic NOEL = 100 ppm nominal (liver cell vacuolation). **Unacceptable** (inadequate numbers of animals at risk, protocol (surgical removal of tumors, use of animals in reproduction study), weekly preparation of diet when test article known to be volatile, inadequate histopathology and blood chemistry); text refers to vacuolated cytoplasm at high dose but no individual histology available. Not upgradeable. Aldous, 11/6/85.

NOTE: Memo of EPA to CDFA reconciling data gap differences (2/3/89) indicates that EPA classifies this study as "supplementary data".

235-011 911217 "Safety Evaluation of Vapona Strips" Summary of 035423.

SUBCHRONIC, RAT

(RELEVANT TO DOSE-SETTING FOR CHRONIC RAT STUDIES)

235-094 074932 "13-Week gavage toxicity study with DDVP in rats". Hazleton Laboratories America, Inc., Madison, WI, 12/28/88. Ten rats (CrI:CD®(SD)BR) per sex per group, dosed by gavage in deionized water vehicle for 5 days/wk, 13 weeks. Dose levels of 0, 0.1, 1.5, and 15 mg/kg/dose. Test article = Dichlorvos, Lot No. 902097, purity 98.3%. **No adverse effects indicated.** Findings associated with cholinergic activity included frequent salivation and urine staining during the period shortly after dosing in 15 mg/kg males and females. NOELs for cholinesterase (ChE) enzyme inhibition were 0.1 mg/kg in males, and < 0.1 mg/kg in females (slight, but statistically significant decrease of RBC ChE in 0.1 mg/kg females at 14 weeks). Also, at termination, a significant decrease in brain ChE was noted at 15 mg/kg in females (nearly 50% reduction), and a non-statistically significant reduction of lesser magnitude was noted in males. In addition, significant decreases in RBC parameters (RBC count, Hgb, and

HCT) were noted in both sexes at 15 mg/kg, and in males at 1.5 mg/kg. There was very equivocal evidence of ocular effects (phthisis bulbi) and also of slight degree of kidney tubular mineralization; both in 15 mg/kg females. If this study is to be used to set dose levels for a long-term aqueous vehicle gavage study, it would appear that a defensible MTD might be at or near to 15 mg/kg. **Acceptable** as a subchronic study. Aldous, 11/6/89.

CHRONIC TOXICITY, DOG

****235-106 088784**, "A 52-Week Chronic Toxicity Study on DDVP in Dogs", (Victoria F. Markiewicz, M.P.H., Hazleton Laboratories America, Inc., Vienna, VA., Study # 2534-102, 8/6/90). DDVP Technical, 97.3% to 99.5% purity relative to an analytical standard, administered orally in gelatin capsules for 52 weeks at 0 (gelatin capsules), 0.05 (0.1 for the first 3 weeks of study), 1.0, and 3.0 mg/kg/day to 4 purebred beagle dogs/sex/group. Chronic NOEL = 1.0 mg/kg/day (increased frequency of emesis in 3 mg/kg/day males and females). Cholinesterase (ChE) NOEL = 0.05 mg/kg/day (dose-related inhibition of plasma and erythrocyte ChE in both sexes at 1.0 and 3.0 mg/kg/day). Also, brain ChE was inhibited significantly in dose-related fashion in 1 and 3 mg/kg/day males, and was also significantly inhibited in 3 mg/kg/day females. **Acceptable. No adverse effects.** H. Green and C. Aldous, 11/14/90.

235-070 035422 "The Effects Exerted upon Beagle Dogs during a Period of Two Years by the Introduction of Vapona Insecticide into Their Daily Diets" (Kettering Lab, 1/19/67). DDVP (dichlorvos, Vapona), 93%; fed in the diet to 3/sex/group at 0, 0.1, 1, 10, 100 or 500 ppm (nominal). Loss of about 64% of test article due to volatility. RBC and plasma cholinesterases were inhibited at 10 and 100 ppm (nominal) respectively to more than 30%, no effect on brain cholinesterase at term. ChE NOEL = 1 ppm; Systemic NOEL = 10 ppm (nominal) based on liver histological changes in females of rarefaction of cytoplasmic substance, enlargement of cells and prominence of cell membrane. **Unacceptable** (limited hematology and clinical chemistry, dose levels not adequately defined for actual exposure, inadequate tissues for histopathology, inadequate number of animals per group.) Mild liver effects without signs in blood chemistry of increase in SGOT, SGPT and alkaline phosphatase. Blood cholinesterases were inhibited but no behavioral signs were reported. Aldous 11/4/85.

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/3/89) notes EPA classification as "minimum".

235-011 035323 "Safety Evaluation of Vapona Strips". Summary of 035422.

CHRONIC TOXICITY, PIG

NOTE: At least 2 chronic pig studies have been performed. One was apparently completed in 1959 by Harris Laboratories. The volume containing the latter study (029:911216) has been lost, and no CDFA [now DPR] review has been performed. The second study was by Bio/Toxicological Research Associates, 1966. DPR has no report for this study, but it is referenced in 088:065499, p. 23. This brief summary does not indicate any adverse effects. There is no present indication that more information on chronic pig studies is necessary, particularly considering that a replacement dog study is completed. C. Aldous, 11/14/90, 12/07/92.

ONCOGENICITY, RAT

****235-095 074933** "NTP technical report on the toxicology and carcinogenesis studies of dichlorvos (CAS No. 62-73-7) in F344/N rats and B6C3F1 mice". Southern Research Institute, April, 1989. Tech. Vapona® [DDVP, dichlorvos], lot SDC 092179, Shell Development Co, Houston, 99% purity. 0, 4, or 8 mg/kg/day, 5 days/wk, to F344/N rats by corn oil gavage for 24 months. No NOEL was identified, however the dosage range was justified. **Possible adverse effects:** Principal indications of treatment-caused neoplasia were increased multiplicity of pancreatic exocrine cell adenomas in males (no increase in numbers of rats affected per group, but an increase in rats with multiple exocrine cell tumors in pancreas) and increased numbers of mononuclear cell leukemias in males. Both are comparatively common tumor types in males and both are considered to be **equivocal** evidence of oncogenicity. Also there was a minor increase in incidence of mammary gland fibroadenomas in females (not dose-related). No marked systemic toxicity. **Acceptable for rat oncogenicity** data requirement. C. Aldous, 10/17/89, 4/18/90 (rebuttal response).

235-050 (no record number). Rebuttal letter of 2/20/90 addressing study 235-095 074933, above. See CDFA response of 4/18/90.

235-081 069616 "A review of the interpretation of the NTP toxicology and carcinogenesis studies of dichlorvos (NTP Technical Report No. 342)". Date of submission of this review by John M. Mennear, Ph.D.: 6/30/88. [Date of galley draft of the referenced NTP report: April, 1989]. Dr. Mennear presented reasons why data on mononuclear cell tumors in male (M) rats, mammary gland tumors in female (F) rats, and pancreatic acinar tumors in M and F rats should collectively indicate only "equivocal evidence" of oncogenicity to rats, in contrast to the NTP Peer Review Panel conclusion of "some" evidence for M and "equivocal" evidence for F. Mouse forestomach tumors were also discussed, however the main focus of this discussion was lack of comparable effects on rats. The CDFA worksheet discusses major issues. No change in study status. C. Aldous, 10/24/89.

235-081 069617 "Mononuclear cell leukemia and pancreatic acinar-cell neoplasia in male F 344/N rats: A review of NTP study interpretations". Date of submission of this review by John M. Mennear, Ph.D.: this review of NTP interpretations was presumably prepared after 6/30/88. [Date of galley draft of the referenced NTP report: April, 1989]. Dr. Mennear presented reasons why the male rat incidence data for mononuclear cell leukemia and for pancreatic acinar-cell tumors should not be considered to represent "some evidence" of carcinogenicity. Salient points of Dr. Mennear's arguments and comments by this CDFA reviewer were noted for CDFA Health Assessment Group consideration. No change in study status. C. Aldous, 10/25/89.

235-094 074930 "Is dichlorvos a carcinogenic risk for humans?", Bremmer, J. N., et al., Mutation Research 209:39-44 (1988). This is a brief discussion of the overall data base for oncogenicity of DDVP. The conclusion of the authors was that DDVP "does not present a carcinogenic or mutagenic risk for man". Since the principal indications of oncogenic potential arise in the recent gavage NTP studies, which have been discussed in detail by Dr. Mennear, above, there is no need for a CDFA "review" of this record. Aldous, 10/26/89.

235-088 065499 "Dichlorvos: A review of carcinogenicity and mutagenicity studies". Several studies were discussed. Primary attention was given to the NTP studies in rats and mice

(1989). Arguments for not assigning concern for oncogenic potential are comparable to those of Mennear, which have been reviewed by CDFA (Records 069616 and 069617). There is no apparent need for a separate CDFA review of this review paper. C. Aldous, 10/26/89.

235-089 067208 "Brief opinion on 'Board Draft' version of NTP Technical Report on toxicology and carcinogenesis studies on dichlorvos", 7/6/87, Dr. F.J.C. Roe. Major points are summarized in a review by C. Aldous, 10/27/89.

235-089 067209 "Comments on the Board Draft NTP Technical Report on the toxicological and carcinogenesis studies on dichlorvos [Report NTP TR 342 Draft 7/87]. Prof. P. Grasso, 7/9/87. There is comparatively little new in this opinion statement which has not been addressed in other opinions. No Data Review Group review is needed. C. Aldous, 10/27/89.

235-050 088033 Blair, D., et al. "Two year inhalation exposure of rats to Dichlorvos vapour". Tunstall Laboratory, June, 1974. Inhalation exposure was nearly continuous (rats were removed from chambers only once daily for inspection) over two years at dosages of 0, 0.05, 0.5 or 5.0 mg/m³ of DDVP vapor) for groups of 50/sex rats (Carworth Farm E strain). **No adverse effects were indicated.** A cholinesterase (ChE) NOEL of 0.05 mg/m³ was observed in males. There was no ChE NOEL in females (slight inhibition of RBC ChE in low dose females). The NOAEL for other effects was 0.5 mg/m³ in both sexes (based primarily on decreased body weights in high dose males and females). The study is **not acceptable, and not upgradeable, but provides useful data:** A major deficiency was that the high dose appeared to have been slightly above the MTD [based on the high dose level "altering the normal life span" (lengthening) in both sexes]; yet the next lower dose was 10-fold lower, hence apparently well below the MTD. Thus there was no optimal high dose exposure. Aldous, 4/26/90.

NOTE: This study was recently re-examined by EPA and classified as "Minimum" for chronic and oncogenicity data gaps (EPA review dated 8/9/89 in Document No. 235-050, preceding text of the study report).

235-071 035425 "Bioassay of Dichlorvos for Possible Carcinogenicity" (Gulf South Res. Inst. for NCI, 1977) Dichlorvos technical, minimum purity 94%; fed in the diet for 80 weeks, followed by 30-31 weeks observation. Group sizes of 10/sex for concurrent controls (60 per sex for "pooled" controls) and 50/sex/test group at 150 or 300 ppm (the latter dosage began at 1000 ppm, but was lowered after 3 weeks because of excessive toxicity). Strain: Osborne-Mendel. Systemic NOEL = 150 ppm (body weight decrements). **No evidence for oncogenicity effect reported. Unacceptable** (no analysis of diet, no individual data, concurrent controls inadequate in number, staggered start for low and high doses with 4-week interval.) Gee, 1/20/87, C. Aldous, 6/1/89 (see note below).

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/3/89) notes EPA classification as "supplementary".

NOTE: study 071:035425 is referenced in the 2/17/88 review prepared for Amvac Chemical Corp. entitled "Dichlorvos: A review of carcinogenicity and mutagenicity studies", CDFA record No. 088:065499, pp. 18-22. The Amvac review was prepared in response to EPA reviews, and addressed 3 aspects of study design: (1) the use of only two dosage groups, (2) administration for 80 weeks instead of the full duration of the study, and (3) use of matched control groups of small size in conjunction with pooled control groups for comparison with treatment groups. This study and the 1/20/87 CDFA review were examined by C. Aldous. A concern previously stated

in the 1/20/87 review about animals being in "poor condition" at term does not appear to reflect a husbandry problem, since geriatric animals would be expected to reflect signs of aging, and since survival was very good in both treatment groups to termination. This study employed animals which were purchased from Charles River, Wilmington, MA. These were third generation offspring from Battelle Memorial Institute Osborne-Mendel stock. The pooled controls were purchased from Battelle Memorial (p. 7). Investigators felt that "there was probably no significant genetic drift influencing the incidence of tumors" (p. 11). Since EPA has recently examined the long-term rat study data base for DDVP, the Registrant is encouraged to submit EPA reviews of all these studies to CDFA. C. Aldous, 5/31/89, 10/27/89, 4/18/90.

235-057 911218 Partial duplicate of 071:035425-035426.

235-081 069614 "Studies on carcinogenicity of DDVP (2,2-dichlorovinyl dimethyl phosphite) mixed in drinking water in rats". Biosafety Research Center, Shizuoka, Japan. 12/2/78. DDVP, grade and purity not provided, at 0, 14, or 28 mg/kg/day nominal dosages, administered in aq solution, to F344 rats for 104 weeks. There were no definitive treatment effects, except that male body weights were reduced at 28 and possibly at 14 mg/kg/day. Apparent NOELs are 14 mg/kg/day for M and 28 mg/kg/day for F. Study **did not demonstrate adverse effects**, however there was a slight increase in mononuclear cell leukemias in males. Incidence was 2, 6, and 6 for controls, 14, and 28 mg/kg/day groups: this was **not** statistically significant by standard two-group comparisons such as Fisher's exact test, but was noteworthy because an increase in male mononuclear cell leukemias was noted in a recent NTP study employing F344 rats. **Not acceptable**. C. Aldous, 5/24/89.

235-081 069615 "Stability of DDVP in drinking water". Brief document by T. Leafe and W. Feiler, indicating that DDVP is stable for some days in acidic or neutral water, and that hydrolysis of DDVP lowers water pH, limiting the further breakdown of DDVP in all but highly buffered, alkaline water. Also, the vapor pressure of DDVP was noted to be much lower than that of water. This document was submitted to show that dosages used in the above study (081:069614) were stable under conditions of the study. Aldous, June 1989.

ONCOGENICITY, MOUSE

****235-095 074933** "NTP technical report on the toxicology and carcinogenesis studies of dichlorvos (CAS No. 62-73-7) in F344/N rats and B6C3F1 mice". Southern Research Institute, April, 1989. Tech. Vapona® [DDVP, dichlorvos], lot SDC 092179, Shell Development Co, Houston, 99% purity. 0, 10, or 20 mg/kg/day (M) or 0, 20, 40 mg/kg/day (F), 5 days/wk, to B6C3F1 mice by corn oil gavage for 24 months. Cholinesterase inhibition was seen at all doses of DDVP. The high doses in males (20 mg/kg/day) and in females (40 mg/kg/day) were apparent LELs for forestomach papillomas (**possible adverse effect**). There was no definitive other toxicity, hence the apparent NOEL for lesions outside of the forestomach is 20 mg/kg/day (male) or 40 mg/kg/day (female). **Acceptable** for the mouse oncogenicity data requirement. C. Aldous, 10/18/89.

235-071 035426 "Bioassay of Dichlorvos for Possible Carcinogenicity" (Gulf South Res. Inst. for NCI, 1977). Dichlorvos technical, 94%, fed in the diet for 80 weeks plus 13-14 weeks of observation; 10/sex for concurrent controls (plus pooled control groups of 100 males and 80 females) and 50/sex/treatment group at 300 or 600 ppm, changed from 1000 and 2000 ppm,

respectively, after 2 weeks because of toxicity. Systemic NOEL = 300 ppm (body weight), oncogenicity effect equivocal due to lack of control data for esophageal tumors. **Unacceptable** (no individual data, inadequate number of animals in concurrent control, no analysis of diets, two doses only.) Gee, 1/20/87.

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/3/89) notes EPA classification of the 1977 NCI study as Supplementary.

REPRODUCTION, RAT

****235-118 117629** "Two-Generation Reproductive Toxicity Study of DDVP Administered in the Drinking Water to CD® (Sprague-Dawley) Rats", (R.W. Tyl *et al.*, Reproductive and Developmental Toxicology Laboratory, Center for Life Sciences and Toxicology, Chemistry and Life Sciences, Research Triangle Institute, Research Triangle Park, NC., Report # 60C-4629-170, 31 August 1992). Production batch dichlorvos, 96.86% pure, Lot #802907. 30 albino CD® (Sprague-Dawley) CrI:CD®(SD)BR rats/sex/group were exposed to the test article in drinking water ad libitum continuously throughout the study (except for F1 females during mating for the F2b litters) at concentrations of 0, 5, 20, and 80 ppm. Rats were exposed for 10 and 11 wk in the pre-mating growth phases, respectively, for the F0 and F1 animals. A separate group of untreated males was used to sire the F2b litters in response to generally poor reproductive performance during production of the F2a litters. Parental NOEL (excluding cholinesterase) = 20 ppm (reduced water consumption in both sexes in both generations during most of the study, reduced body weights in F1 parents). Reproductive NOEL = 20 ppm [reduction in numbers of F1 dams pregnant, estrous cycling was not evident or was irregular in F1 females (not assessed in F0 females)]. Strictly speaking, there was no cholinesterase NOEL, due to small but statistically significant reductions at 5 ppm (RBC and plasma cholinesterase in F1 males, RBC cholinesterase in F0 and F1 females). Nevertheless, a practical NOAEL of 5 ppm is supportable for meaningful cholinesterase effects. At 20 and 80 ppm there were consistent, dose-related decrements in plasma, RBC and brain cholinesterase. No specific cholinergic signs were observed at any dose in this study. **Acceptable. No adverse effects.** (H. Green and C. Aldous, 12/11/92).

235-105 088543 Draft results of range-finding two-generation study, undertaken prior to the definitive study in Document No. 235-118, above.

Pages only, no record number, ID # SBC-131759-E, 11/22/91 Letter from D. Allemang, Jellinek, Schwartz, Connolly and Freshman, Inc., referring to the ongoing two-generation reproduction study, being conducted at Research Triangle Institute with DDVP. Data at this point suggested possible effect on testicular degeneration (but not on testicular atrophy). No worksheet. Gee, 6/30/92. (See DPR review for Document No. 235-118, above).

235-117 114476 Follow-up letter on the two-generation reproduction study in progress from D. Allemang, dated 2/20/92, (data not subjected to QA as of this date. Vaginal cytology data were presented (see DPR review for Document No. 235-118, above).

235-073 035434 "The Effects Exerted upon the Fertility of Rats and upon the Viability of Their Offspring by the Introduction of Vapona Insecticide into Their Diets" (Kettering Lab, 4/12/65). DDVP (dichlorvos, Vapona), 93% by weight, fed in the diets of CD rats, 15/sex/group, at 0, 0.1, 1, 10, 100 or 500 ppm for the first generation. There were 10 males 20 females per group for

next two matings. Rats were dosed for six weeks before first mating for F1a litter; then mated with 3 males and 3 females per cage for F1 litters (cannot determine mates - group mating unacceptable). There were single litters in F2 and F3 generations. NOEL \geq 500 ppm; no adverse reproductive effect reported. **Unacceptable** (dose selection unjustified: no evidence of toxicity, no analysis of diet (test article is known to be volatile and unstable in feed, yet the feed was prepared at weekly intervals), no individual data, no histopathology of adults of F1 or subsequent generations.) C. Aldous, 11/7/85, 5/26/89 (see concurrent rebuttal document).

TERATOLOGY, RAT

235-072 035428 "Toxicity Studies with Dichlorvos: Teratogenic Studies in Rats and Rabbits given Dichlorvos by Inhalation" (Tunstall Lab, 7/71, TLGR.0035.71). DDVP (dichlorvos), 97%. 16 rats in control group and 9 - 10 in each of treated groups. Treatment by inhalation, 23 hours/day, 7 days /week, at 0, 0.25, 1.25 or 6.25 ug/l nominal. Dose range appeared to be valid, judging by maternal cholinesterase (ChE) inhibition in RBC's, plasma and brain at 1.25 mg/l and above. No developmental toxicity reported. **Unacceptable** (too few litters per group, conditions of exposure not defined adequately for particle size, air flow, stability of test article during exposure, no individual data). Aldous, 11/8/85.

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/3/89) notes EPA classification as "supplementary".

**235-110 096391, R.W. Tyl, M.C. Marr, and C.B. Myers, "Developmental Toxicity Evaluation of DDVP Administered by Gavage to CD® (Sprague Dawley) Rats", RTI-60C-4629-10/20, Research Triangle Institute, Research Triangle Park, NC, 02/22/91. Twenty-five, mated (sperm positive = gestation day 0), female CD® (Sprague-Dawley) rats / dose were exposed on gestation days 6 through 15 by single daily oral gavages to DDVP (lot # 802097, 97% purity, water vehicle) at 0.0, 0.1, 3.0, or 21 mg/kg/day and sacrificed on gestation day 20. Treatment-related maternal effects were tremors and decreased food consumption and weight gain at 21 mg/kg/day. Maternal lethality (2/8) at 30 mg/kg/day and a NOEL for RBC and plasma ChE inhibition (0.1 mg/kg/day) were demonstrated in a pilot study. There were no treatment-related fetal effects. No adverse effect was indicated (maternal NOEL = 3 mg/kg/day \leq fetal NOEL \geq 21 mg/kg/day). The study was acceptable (S. Morris, 07/03/91).

TERATOLOGY, RABBIT

235-072 035432 "Teratogenic Potential of Dichlorvos given by Inhalation and Gavage to Mice and Rabbits" (National Institute of Environmental Health Sciences, 1979, publication in Teratology 20: 383-388 (1979) by B. A. Schwetz et al.) Dichlorvos, 96%, Batch no. 12-MMV-10. A gavage study involved dosages of 0 or 5 mg/kg/day to New Zealand White rabbits. There were 8 control litters and 12 test litters. The inhalation study involved exposure to 0 or 4 mg/l 7 hr/day (measured). There were 14 control litters and 19 exposed litters. No adverse effects were indicated. **Unacceptable** (no individual data, single dose per route at stated MTD but no clinical signs were observed.) The rabbit teratology data requirement may be subsequently filled, considering supportive information from the Tunstall Labs studies (072:035427), on receipt of

individual data from the study published by Schwetz et al. C. Aldous, 10/23/85, 5/26/89.

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/3/89) notes EPA classification as "supplementary".

235-072 035430 "Teratological Studies with Dichlorvos in Rabbits" (Food and Drug Res. Labs, 6/30/69). Dichlorvos, no purity stated; given orally incorporated into polyvinyl chloride resin in capsules at 0, 3, 12, 36 and 60/24 (reduced for 7 1/2 days) mg/kg/day, days 6 - 16 of gestation, 15 rabbits/group; 3 mg/kg dose added later. Litters/group: 11/15 in control, 8/15 in 12 mg/kg group and 12/15 at 3 mg/kg dose; no litters at 36 or 60/24 mg/kg. No NOEL can be established from study. **Unacceptable** (too few pregnant does, inadequate data for maternal toxicity, test article not described adequately, possible confounding effect of PVC resin, maturity of does not clear.) No teratogenic effect reported but inadequate for evaluation. Aldous, 11/12/85.

NOTE: This study was not available to EPA for review.

235-072 035429 "Teratology Studies in Rabbits" (Food and Drug Res. Labs, 6/30/69). DDVP (dichlorvos) given in capsules with polyvinyl chloride resin; 26 in control and 15, 15 and 20 in low (12 mg/kg), mid (36 mg/kg) and high (62 mg/kg) groups, days 6 - 18. NOEL cannot be determined. **Unacceptable** (test article not characterized and actual levels administered not clear, too few pregnant animals per group with many stated as "immature", top dose subdivided into two groups and exposed for only part of organogenesis, too many deaths.) Aldous 11/8/85.

NOTE: This study was not available to EPA for review.

235-072 035431 Interpretative commentary on 035429 and 035430, above.

235-072 035427 "Toxicity Studies with Dichlorvos: Teratogenic Studies in Rats and Rabbits given Dichlorvos by Inhalation" (Tunstall Labs, 7/71, TLGR.0035.71). DDVP (dichlorvos), 97%, by inhalation 23 hours/day, 7 days/week, days 1 - 28 of gestation. Dutch rabbits, 19-20 per group at 0, 0.25, 1.25 or 6.25 ug/l nominal. 16/20 died in high dose group. In a second trial, doses of 0, 2 and 4 ug/l were used with 13-16 per group. ChE NOEL = 0.25 ug/l. Developmental toxicity NOEL not determined from study. **Unacceptable** (inadequate numbers of fetuses for evaluation - fetuses were examined for either skeletal or visceral findings - not both, conditions of exposure not thoroughly described, no corpora lutea counts, early and late fetal deaths not distinguished.) There was an apparent increase in late gestational fetal deaths at 4 ug/l, but this toxicity may have been due to technical problems: actual exposure in this group reached 6.6 mg/l for a time, and 6/20 dams died or were killed in extremis in this group. Aldous, 11/8/85.

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/3/89) notes EPA classification as "minimum".

235-090 068132 An omnibus collection of interpretative summaries of studies. This collection is listed here because several rabbit teratology studies were reviewed. Some of these comments were considered in the 5/31/89 CDFA Rebuttal Response (C. Aldous, 6/1/89).

**235-111 096392, "Developmental Toxicity Evaluation of DDVP Administered by Gavage to

New Zealand White Rabbits", RTI-60C-4629-30/40, Research Triangle Institute, Research Triangle Park, NC, 02/22/91. Sixteen, artificially-inseminated (gestation day 0), female New Zealand White Rabbits/dose were exposed on gestation days 7 through 19 by single daily oral gavages to DDVP (lot # 802097, 97% purity, water vehicle) at 0.0, 0.1, 2.5, or 7.0 mg/kg/day and sacrificed on gestation day 30. Treatment-related maternal effects were clinical signs of cholinesterase inhibition and decreased food consumption at 7.0 mg/kg/day and lethality at 2.5 (2/16) and 7.0 mg/kg/day (4/16). A pilot study demonstrated lethality (5/8) and NOEL for RBC and plasma ChE inhibition (0.1 mg/kg/day). There were no treatment-related fetal effects. No adverse effect was indicated (maternal NOAEL = 0.1 mg/kg/day \leq fetal NOAEL \geq 7.0 mg/kg/day). The study was acceptable (S. Morris, 07/10/91).

TERATOLOGY, MOUSE

235-072 035433 "Teratogenic Potential of Dichlorvos given by Inhalation and Gavage to Mice and Rabbits" (National Institute of Env. Health Sciences, publication in Teratology 20: 383 - 388 (1979) by B. A. Schwetz *et al.*) Dichlorvos, 98%, Batch No. 12-MMV-10; mice were given 60 mg/kg/day by gavage with 28 control litters and 25 exposed litters; in a second series, mice were exposed to 4 ug/l 7 hr/day, by inhalation with 20 litters in the controls and 15 litters in the exposed group; no developmental effect was reported. **Unacceptable, does not appear to be upgradeable** (single dose, no individual data, although stated to be the maximum tolerated doses, no toxicity was reported.) Additional information will be examined (if submitted) on the mouse segment of this study, since the Registrant will probably be sending information on at least the rabbit segment of this study. Aldous, 11/12/85.

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/3/89) notes EPA classification as "supplementary".

TERATOLOGY, GUINEA PIG

No document number, no record number. "The Effect of Trichlorfon and other Organophosphates on Prenatal Brain Development in the Guinea Pig" (Mehl, A., Schanke, T. M., Johnsen, B. A., and Fonnum, F., *Neurochemical Research* 19: 569-574 (1994). Dichlorvos (99%) was given to guinea pigs i.p. [?] as follows: 15 mg/kg/day, single dose on days 42, 43 and 44 of gestation; 15 mg/kg, twice daily at 12h intervals, days 42, 43 and 44; 15 mg/kg, twice daily at 12h intervals, days 44, 45 and 46. There was a single pregnant dam per dosing regimen and one litter of pups (4 in each litter) was analyzed for the effect on the brain weight. Other organophosphates also tested were trichlorfon (125 mg/kg, days 42,43 and 44), ethyl-trichlorfon (125 mg/kg/day, days 44, 45 and 46), ethyl-trichlorfon (138 and 121 mg/kg/day, days 42 and 44), soman and TOCP. The pups were weighed and the brain recovered within 24 hours of natural birth. The brains were weighed and dissected into: medulla, cerebellum, quadrigemina, hippocampus, cerebral cortex and diencephalon. Each region was weighed. Selected regions (cerebellum, medulla and cerebral cortex) were homogenized and assayed for activity of glutamate decarboxylase, choline acetyltransferase and acetyl cholinesterase. The results showed that treatment with trichlorfon and dichlorvos (at 15 x 2 doses per day) during gestation days of the brain growth spurt caused significantly lower total brain weight and lower weight for selected regions of the brain. There was no effect on enzyme activity. **Possible adverse effect.** The study and report contain deficiencies including a single dam per dosing regimen

and missing details of methodology. The study is **supplemental**. (Gee, 6/12/98)

GENE MUTATION

Microbial Systems

235-075 035438 "The Mutagenic Effect of Organophosphate Insecticides on *E. coli*" (Tunstall Lab for SDS Biotech, 8/71) Dichlorvos was one of nine insecticides tested with *E. Coli* B/r WP2, plated in triplicate with no adverse effect reported. **Unacceptable** (no data, no dose level stated.) Gee, 11/13/85.

235-075 035443 "Mutagenicity of Some Organophosphorus Compounds at the *ade6* Locus of *Schizosaccharomyces pombe*" (Laboratoire de Genetique, Belgium, publication in Mutation Res. 117: 139 - 148 (1983)) DDVP (dichlorvos), >99%; strain SP-198 *ade6-60*/rad 10-198/h⁻¹, exposed for 1 hour to approximately 1.5, 4 or 14 mM (from graph); with and without mouse liver activation, replicates not stated; table indicates LD50 as 5.5 but no data; concentration-dependent increase in mutants; **unacceptable** (number of plates not specified, no individual colony counts, inadequate description of test.) Gee, 11/14/88.

235-075 035444 "Activity of OP Insecticides in Bacterial Tests for Mutagenicity and DNA Repair - Direct Alkylation versus Metabolic Activation" (Zentralinstitut für Genetik and Kulturpflanzenforschung, 8/7/81, publication in: Chem.-Biol. Interactions 39: 339 - 0350 (1982). DDVP (dichlorvos), 99%; tested with *Salmonella* strains TA1535, TA1537, TA1538, TA98 and TA100, with and without activation with NMRI mouse liver; tested at 5, 10, 20 or 40 µM/plate, duplicate plates; cytotoxicity with TA100; replicate trials; increase in reversion reported in

TA100 only without activation; **unacceptable** but possibly upgradeable (individual plate counts and replicates, clarification of "µM/plate" is needed.) Gee, 11/14/85.

Mammalian Systems

****235-083 050037** "L5178Y TK +/- Mouse Lymphoma Forward Mutation Assay with Dichlorvos" (Microbiological Assoc., 10/14/86, T-5211.702003, Doc. No. 132\12-86-0036-TX-002) Mouse lymphoma; Dichlorvos, 97.5%, lot 11381-23-5, liquid; tested with and without rat liver activation, two acceptable trials each; without activation, at 0 to 0.33 in trial 1 and 0 to 0.12 µl/ml in trial 2; with activation, at 0 to 0.24 µl/ml in trial 1 and 0 to 0.12 µl/ml in trial 2; increase in mutation frequency to greater than twice control in \pm activation, especially without activation; **acceptable with a possible adverse effect for gene mutation**. Gee, 1/20/87.

235-080 037219 "A Synopsis of a Mouse Lymphoma Forward Mutation Assay with Dichlorvos" (NIEHS/NTP, Litton Bionetics, 8/27/85, 5TX-85-0065) Dichlorvos, no purity stated; mouse lymphoma L5178Y TK +/-, clone 3.7.2C, tested without activation at 0, 6.25, 12.5, 25, 50, 100 or 200 nL/ml for 4 hours with cytotoxicity at > 50 nL/ml; concentration-related increase in mutation frequency at the three lowest exposures; **unacceptable** (no metabolic activation included, no purity of test article.) Gee, 2/3/86.

SUMMARY: The two mutagenicity studies in mammalian cells confirm each other for positive

activity. The evidence in microbial systems is less certain with only one (TA100) of five strains of Salmonella responding positively. Gee, 11/88.

NOTE: The potential for mutagenicity in maximally dosed mammals is acknowledged, and must be noted as a "possible adverse effect". A relevant submission entitled "Discussion of the mutagenic potential of dichlorvos" [which begins on p. 29 of record #s 088:065499 and 090:068132 (this section of either record is identical)] should be examined by Health Assessment Section when the relevance of mammalian mutagenicity studies is assessed. The major point of this discussion is that dichlorvos metabolism generally proceeds by an esterase-catalyzed pathway, but when that pathway is saturated by heavy dosing, an alternative demethylation pathway becomes significant. Dr. Bernard (author of this discussion) suggests that the esterase cleavage products are likely to be less mutagenic than the demethylation products, and that the esterase products represent the relevant pathway for chronic human health risk assessment. This CDFA reviewer (C. Aldous) does not agree with the subsequent implication (see p. 29) that the esterase product, dichloroacetaldehyde, is a lesser concern because of its "extremely transient existence". On the contrary, this transience may attest to a high level of biological activity, with mutagenic potential. Unless the reactive molecule or molecules which are responsible for mutagenicity are identified, and demonstrated to be not significant intermediates in human metabolism, it would appear that the mutagenicity demonstrated in the above studies may not be discounted. Incidentally, Aquilina et al. (1984, CDFA [DPR] volume/record No. 075:035440) referenced two studies showing dichloroacetaldehyde to cause gene mutations in microorganisms and one study which found dichloroacetaldehyde to cause dominant lethal mutations in mice. C. Aldous, 6/2/89.

CHROMOSOME EFFECTS

235-080 037224

235-080 037225 "A Dominant Lethal Assay in Mice with T-169-1" (Microbiological Assoc., 10/2/85, Study 695-5TX-85-0004) Dichlorvos, 98.4%; injected intraperitoneally for 5 consecutive days to 10 males per group at 0, 1, 3 or 10 mg/kg/day; mated each to 2 females/week for 8 weeks; TEM as positive control; no evidence of a dominant lethal effect; **unacceptable** (inadequate number of pregnant females, no explanation for 0% fertility in positive control group, no justification of dose selection.) Gee, 2/3/86.

235-075 035437 "Toxicity Studies with dichlorvos: Investigation of the Dominant Lethal Mutation Potential in the Mouse after an Inhalation Exposure" (Tunstall Lab, 5/71). DDVP (dichlorvos), technical, purity > 97%, given by inhalation at 30 or 55 ug/l (nominal) for 16 hours to 16 control males, and 8 males per treatment group. Each male mated to 3 females weekly for 8 weeks. Increase in early fetal deaths in week 6 of 8 weeks. **Unacceptable** (actual concentration measured but data not included, inadequate number of treated males, no justification for dose selection, no description of exposure conditions.) Gee, 11/13/85.

235-075 035439 "Toxicity Studies with Dichlorvos: Investigation of the Dominant Lethal Mutation in the Mouse after Multiple Inhalation Exposures" (Tunstall Lab, 8/71) DDVP (dichlorvos) technical, > 97%, given by inhalation 23 hours/day, 4 weeks, to 16 males in control and 8 males in each treatment group, at 2.1 or 5.8 ug/l (nominal); CF1 mice; treated males mated to 3 females weekly for 8 weeks; no deaths, no adverse effect reported; **unacceptable**

(inadequate number of treated males, no justification of dose, no description of inhalation conditions, actual concentration measured but not reported, no individual data, no rationale for route of exposure.) Gee, 11/13/85.

235-075 035441 "Cytogenetic Effects induced by Organophosphorus Pesticides in Mouse Spermatocytes" Laboratoire de Genetique, Belgium, publication in Toxicology Lett. 21: 315-319 (1984). DDVP (dichlorvos), given in a single i.p. injection at 10 mg/kg, 14 organophosphorous compounds tested; cytogenetic effects analyzed after 10-15 days in primary spermatocytes; 500 spermatocytes per animal; no increase in aberrations reported at any of three time intervals. **Unacceptable** (incomplete). Gee, 11/14/85.

235-075 035442 "Cytogenetic and Genetic Effects of Subchronic Treatments with Organophosphorus Insecticides" [Lab de Chimie Medicale, Belgium, publication in: Arch. Toxicol. 56: 66-67 (1984)]. DDVP (99%) given in the drinking water at 2 ppm (maximum residue allowed in Belgium) for 7 weeks to male mice; analyzed bone marrow and sperm for aberrations; no adverse effect reported; also included a dominant lethal assay with 20 males at same exposure mated to 4 females each for 1 week - no adverse effect reported. **Unacceptable** (incomplete report.) Not upgradeable. Gee, 11/14/85.

235-075 035446 "Test of Dichlorvos using the Sensitive-indicator Method for Dominant Skeletal Mutations in Mice" (Oak Ridge Nat. Lab, 3/82, publication in: Environmental Mutagenesis : 115 (1982). Abstract. Male and female mice were exposed to a resin strip impregnated with dichlorvos for 80 days before mating; scored fetal skeletons for effects - none reported. **Unacceptable** (protocol). Gee, 11/14/85.

**235-080 037220

235-080 037221 "A Micronucleus Test in the Mouse using Dichlorvos" (Microbiological Assoc., 9/27/85, Study 695-5TX-83-0095-000) Dichlorvos, 98.4%; 5/sex/group/sacrifice interval injected i.p. with 0, 4, 13 or 40 mg/kg body weight twice at 24 hour interval, sacrificed at 30, 48 or 72 hours; LD50 approximately 56 mg/kg; 2 males and three females died at 40 mg/kg; no evidence of micronucleus formation. **Acceptable**. Gee, 2/3/86.

235-084 055463 "A Dominant Lethal Assay in Mice with Dichlorvos" (Microbiological Associates, Inc., 3/9/87). Dichlorvos, 97.5%, administered intraperitoneally to male CD-1 mice at dosages of 0 (corn oil), 8, 16 or 32 mg/kg/day on each of 5 consecutive days, 30/group, 35/high group. Mated 1:2 weekly for 8 weeks. TEM was positive control. No adverse effect reported. **Acceptable. Shimer & Luthra 10/87.

CHROMOSOME SUMMARY: No adverse effect was reported in an acceptable micronucleus test in mice and no dominant lethal effect was noted in several incomplete reports nor in an accepted replacement study. In addition, several publications reported no adverse cytogenetic effect in mouse spermatocytes or bone marrow. Thus there are no adverse chromosomal effects indicated. Gee, 10/27/87, 6/2/89.

DNA DAMAGE

235-075 035444 "Activity of OP Insecticides in Bacterial Tests for Mutagenicity and DNA

Repair - Direct Alkylation versus Metabolic Activation and Breakdown" (Zentralinstitut für Genetik und Kulturpflanzenforschung, 8/7/81, publication in Chem.-Biol. Interactions 39: 339-350 (1982). DDVP (dichlorvos), no purity stated; Proteus mirabilis, PG 713 and PG 273 with no activation, tested at 10 or 40 uM/plate, with Proteus in top agar and test article added in a well in 0.1 ml ethanol; results reported as "+" for dichlorvos - no data. **Unacceptable** (inadequate data.) J. Remsen (Gee), 11/14/85.

235-075 035440 "Genotoxic Activity of Dichlorvos, Trichlorfon and Dichloroacetaldehyde" Instituto Superiore di Sanita, Italy, publication in: Pest. Sci. 15: 439 (1984). Unscheduled DNA synthesis in human epithelial cells, DDVP (dichlorvos), no purity stated; cells (not a well-identified line/strain), exposed for 1 hour without activation at 0, 1.25, 2.5 or 5.0 mM as confluent monolayers, radioactive thymidine for 4 hours and autoradiography for analysis; also tested CHO V79 for ouabain resistant mutations; **unacceptable** (no activation or justification for not including it, inadequate details of methods, cytotoxicity data, justification for concentration selection, number of cells scored, others.) Positive, concentration-dependent effect for UDS reported for the two pesticides, but not for the dichloroacetaldehyde. Gee, 11/13/85.

****235-080 037222** "An In vivo Sister Chromatid Exchange Assay in Mice with Dichlorvos" (Microbiological Assoc., 9/27/85, Study 695-5TX-85-0003) Dichlorvos, 98.4%; injected once i.p. at 0, 3, 10 or 30 mg/kg into B6C3F1 mice, 5/sex/group; dose selection from preliminary study at doses to 100 mg/kg; sacrifice at 24 hours after injection; scored 50 metaphases per animal; no evidence for increase in sister chromatid exchanges; **acceptable**. Gee, 2/3/86.

235-123 120415 "In vivo Cytogenetics Assay: Analysis of Chromosomal Aberrations in Bone Marrow and Spermatogonial Cells Following Repeated Dose Administration." (Putman, D. L. and E. H. Shadly, Microbiological Associates, MD, Study No. TA458.109001, 12/18/92) Dichlorvos (DDVP), lot 802097, 98.09% purity, was given by oral gavage to 10 male ICR mice per dose at 0 (water), 12.5, 25 or 50 mg/kg body weight/day for 5 consecutive days. Bone marrow cells and spermatogonial cells were collected 24 hours after the last dosing. Dose selection was based on a range-finding study. Fifty metaphases of each cell type were scored per animal when possible. Cyclophosphamide was the positive control and functioned as expected. There was no increase in aberrations in either the bone marrow or the spermatogonial cells with dosing. Study is **unacceptable** and does not appear to be upgradeable (use of one sex only). No adverse effect. Gee, 2/8/93.

SUMMARY: Two in vitro tests give evidence for DNA damage (35444 and 035440) while the in vivo tests are negative. These tests, however, measure different endpoints and are, therefore, not directly comparable. In view of the results under "Gene Mutation", the overall assessment is that DDVP is genotoxic when measured in some systems including mammalian cells. Gee, 10/27/87, 6/2/89, 2/9/93.

MUTAGENICITY, GENERAL

235-066 027075 Summaries of studies in bacteria and fungi demonstrating genotoxic effects. EPA data call-in notice, 1983.

ACUTE DELAYED NEUROTOXICITY, HEN

****235-094 074931** "DDVP: An acute delayed neurotoxic study in chickens". Wildlife International Ltd., 12/29/88. DDVP Technical, Lot #802097, purity 96.5%. White leghorn hens, 42 weeks old, treated by oral intubation with 16.5 mg/kg DDVP in distilled water. Negative control was distilled water; 600 mg/kg TOCP diluted in corn oil was positive control. Dosage volume 8 ml/kg b.w. in all cases. DDVP and negative controls were dosed day 1 and again day 22, and maintained for an additional 21 days. Positive controls were dosed on day 1 only. Sacrifice on day 22 (TOCP positive controls) or 43 (all others). A **possible adverse effect** was noted in histopathological examinations of sciatic nerve: one of 10 DDVP hens had nerve fiber degeneration in the proximal right sciatic nerve, and axonal swelling in proximal and distal parts of that nerve. No negative controls were affected, however 5 of 10 positive controls had nerve fiber degeneration and associated axonal swelling. All TOCP hens had some loss of coordination, and some had apparent lower limb weakness by day 21. Six out of 10 TOCP hens had some motor activity functional deficits consistent with organophosphorous compound - associated delayed distal neuropathy, compared with none of the control or DDVP groups. Study is **acceptable**. C. Aldous, 11/7/89.

NOTE: It is expected that reports of any subsequent neurotoxicity testing performed as a follow-up to this study will be submitted to CDFA for review.

235-074 035435 "Neurological Effects (Demyelination) of Vapona Insecticide on Chickens" (Shell Chemical, Agricultural Chem. Div., 2/18/85.) Hens were treated with 2.5 mg/kg for 5 days/week, 3 weeks. No TOCP-type neurotoxicity was observed. LD50 in hens was estimated to be 22.8 mg/kg. **Unacceptable** (protocol). No adverse effect reported. Aldous, 11/7/85.

NOTE: This study was not available to EPA for review as of 2/3/89.

235-074 035436 "Oral Neurotoxic Potential of Technical Dichlorvos (SD 1750) in the Chicken" (Shell, 5/3/71) Atropinized hens were given 22.9 mg/kg (stated as twice the LD50 - see 035435); 8/10 survived for 30 days. **Unacceptable** (protocol). No adverse effect reported. Aldous, 11/7/85.

NOTE: This study was not available to EPA for review as of 2/3/89.

ACUTE NEUROTOXICITY, RAT

124 120984; Acute Neurotoxicity Study; 818; Rat; WIL Research Laboratories, Inc., Ashland, OH. Dichlorvos (purity 97.87%); 12 animals/sex/group; Doses: 0, 0.5, 35, 70 mg/kg, by gavage; Mortality: 0 (M/F: 0/12), 0.5 (M/F:0/12), 35 (M/F: 0/12), 70 (M:1/11, F:5/12); Observations (signs observed in both sexes at 35 and 70 mg/kg unless noted): Functional Observational Battery-(Home Cage Observations) altered posture, clonic convulsions, whole body tremors, (Handling Observations) constricted pupils, (males only), salivation, increased eye prominence, decreased muscle tone, altered respiration, pale skin, poor grooming, (Open Field Observations) increased mean time to first step, impaired mobility and gait, decreased arousal, decreased rearing, (Sensory Observations) absence of approach response (except for 35 mg/kg females), absence of touch response, absence of tail pinch response, lack of response to olfactory stimuli (70 mg/kg only), absence of pupil response, impaired air righting reflex, (Neuromuscular Observations) reduced hindlimb resistance, reduced grip strength (70 mg/kg only), impaired rotarod performance, increased hindlimb footsplay (70 mg/kg only),

(Physiological Observations) increased duration of catalepsy, decrease in body temperature, Locomotor Activity- reduced motor activity, recovery evident for all parameters by day 7 in all animals; Necropsy, Histopathology (animals which died): reddened cortico-medullary junction in the kidney (M:1/1, F:1/5), no treatment-related lesions in the surviving animals; **adverse effect:** convulsions, tremors; **NOEL**-0.5 mg/kg (based on treatment-related signs in 35 mg/kg group); **Study Supplemental.** (Moore, 7/16/93)

Note: Study was performed according to the 818 guidelines for the evaluation of acute neurotoxicity. Although these results indicate the adverse effects of tremors and convulsions, they were readily reversible and distinguishable from the effects identifiable as those resulting from acute delayed neuropathy.

235-120 117929 Lamb, I.C., "An acute neurotoxicity study of dichlorvos in rats", Wil Research Laboratories, Inc., Study No. WIL-188003, 3/3/92. This study had been submitted in response to U.S. EPA requirements. The report will be reviewed at a later time by another working group in this Branch (the data do not apply at present to "SB-950" requirements). Aldous, 12/8/92.

235-119 117928 Lamb, I.C. (pilot study to 235-120 117929, above).

SUBCHRONIC NEUROTOXICITY

****133 126465** Lamb, I. "A Subchronic (13 Week) Neurotoxicity Study of Dichlorvos in Rats" (WIL Research Laboratories, Inc., Ashland, Ohio; WIL Study 188004, 9/30/93). Dichlorvos (DDVP) technical (lot# 802097, 97.87% purity) was administered orally (gavage) for a minimum of 91 consecutive days (7 days/week) to 15 Sprague-Dawley Crl:CD®BR rats/sex/dose at levels of 0, 0.1, 7.5 or 15 mg/kg/day. High-dose rats had tremors, salivation, exophthalmus, lacrimation, clear material on forelimbs, rales, chromodacryorrhea and material around the mouth. Body weights in the high-dose females were significantly lower than controls by week 13. Inhibition of plasma and RBC cholinesterase (ChE) was noted in the mid-dose and high-dose groups at weeks 3, 7 and 13; brain stem and/or cerebral cortex ChE inhibition ranged from 11-12% in the mid-dose and 10-16% in the high-dose rats at week 13. **No Adverse Effects** were noted in the FOB, locomotor, brain weight/dimension or other neuropathological parameters. NOEL (for systemic effects and ChE inhibition) = 0.1 mg/kg/day. ACCEPTABLE. Kellner and Gee, 1/28/94.

**** 143, 144 133037 & 133245** "DDVP: 28-Day Neurotoxicity in the Domestic Hen," (Manley, A., Huntingdon Research Centre Ltd., Cambridgeshire, UK; 10/21/94; AVC 1/921405). DDVP technical (97.87% pure; Batch #: 802097) was administered by gavage for 28 days to adult female domestic hens (Ross Hi-Sex Brown, Gallus gallus domesticus) at 0 (distilled water), 0.3, 1.0, 3.0 mg/kg (21/dose) and 0.1 mg/kg DDVP (3 hens--added later to determine brain ChE activities at day 30). TOCP (7.5 mg/kg) served as a positive control (21 hens) and corn oil served as vehicle control (4 hens--also used for brain ChE activities at day 30). The birds were observed for a total of 49 or 77 days after onset of dosing. Systemic NOEL = 0.3 mg/kg (Transitional weight loss occurred at 3.0 mg/kg. Unsteady gait and an inability to stand was observed in 2/21 hens at 1.0 mg/kg. At 3.0 mg/kg there were clinical signs of wings outstretched, birds being pecked, limping, inability to stand, quiet/subdued, unsteadiness and death which occurred in 1/21 at 1.0 mg/kg and 4/21 at 3.0 mg/kg.) Neurotoxicity NOEL ≤ 0.3 mg/kg (Axonal degeneration in the cerebellum, spinal cord, sciatic nerve and tibial nerve was

increased at all doses, compared to control. Histopathology (splitting/thickened and/or densely staining material within myelin) was observed at all doses.) ChE NOEL = 0.3 mg/kg (On day 4, brain ChE (BrChE) was inhibited 44% at 1.0 mg/kg and 63% at 3.0 mg/kg. By day 30, BrChE was inhibited 26% at 0.3 mg/kg, 34% at 1.0 mg/kg and 54% at 3.0 mg/kg. Brain neurotoxic esterase (B/NTE) and spinal cord NTE (SC/NTE) were not affected by DDVP treatment. Possible adverse effect (Neurohistopathology was observed at all treatment levels.) Acceptable. M. Silva, 2/6/95.

A letter was submitted by AMVAC Chemical Corporation to contest the adverse health effects observed by DPR in 235-143, 144/133037. No worksheet. M. Silva, 11/30/95

149 137355 "Response to California EPA Department of Pesticide Regulation Medical Toxicology Branch Review of: Dichlorvos (DDVP): 28-Day Neurotoxicity Study in the Domestic Hen," (W.F. Millar, AMVAC Chemical Corporation, City of Commerce, CA, 4/21/95). The volume contained a discussion of the DPR review of this study, specifically the adverse effects flag for DPR volume/record #: 235-143, 144/133037, 1332245 (reviewed above).

235-122 119717 "Dichlorvos (DDVP) 28 Day Neurotoxicity Study in Hens" Preliminary submission as an adverse effects disclosure of data not submitted to Quality Assurance inspection. Twenty-one hens per group were given 0, 0.3, 1.0 or 3.0 mg/kg/day. Birds were sacrificed after 49 or 77 days and sections of brain, spinal cord and peripheral nerves were examined. TOCP was the positive control. At 49 days, 2/6 examined showed minimal axonal degeneration of the spinal cord at 3.0 mg/kg. One bird in each of the 1.0 and 0.3 mg/kg showed minimal degeneration in one level of the spinal cord. At 77 days, 1/5 at 3.0 mg/kg showed minimal axonal degeneration at 2 levels in the spinal cord and 1/6 at 1.0 mg/kg showed an effect. No effect was reported at 0.3 mg/kg. No worksheet. Gee, 2/8/93.

OTHER STUDY TYPES

METABOLISM/DISPOSITION STUDIES

235-101 086302 Jeffcoat, A.R., "Dermal absorption of Dichlorvos in rats". Research Triangle Institute, 3/23/90. This study was reviewed by Robert Zendzian (EPA HED) in a review signed off on 5/7/90. Study was classified as "Acceptable". Conclusions: "Dermal doses of 0.3, 3.0 or 30 ug/cm², 10 hour wash and total exposures of 10, 24, and 120 hours per dose. 9.4 to 11.44% of the dose was absorbed, 12.1 to 20% of dose remained on skin after washing and 37.7 to 51.5% of the dose evaporated during the 10 hour exposure before washing. There was no dose or time relationship shown for any of these parameters." EPA review conclusions were recorded by Aldous, 7/5/90. Subsequently, CDFA WHS Branch reviewed the study, and classified it as "acceptable", recommending that 13% dermal absorption be used for human exposure.

Miscellaneous documents in alphabetical order by authors.

[No record number] Anonymous, 1967. Safe use of pesticides in public health. WHO Technical Report Series 356, WHO, Geneva, p. 46-54. "8. Safety of dichlorvos (OMS-14) for disinfection of aircraft." The use of impregnated filters with compressed air to maintain a

concentration of 0.2 - 0.25 ug/liter of air for ½ hour in airplanes for insecticidal use was discussed. The pharmacological activity is through inhibition of cholinesterase without causing permanent neurotoxicity. Results of a number of publications in which human populations were exposed to dichlorvos under several conditions were reviewed in brief. Cholinesterase activity was the primary parameter measured during exposure. A number of these publications have been examined by Medical Toxicology and are described in this "Summary of Toxicology Data." The conclusion of the report authors was that dichlorvos exposure to concentrations effective against insects (0.15 - 0.25 ug/liter of air for 30 minutes) would not produce adverse effects. (Gee, 5/25/99)

[No record number] Boyer, A. C., 1975. Inhibition of human plasma cholinesterase by steady-state concentrations of dichlorvos. (Shell, Consumer Products, Technical Progress Report No. M-44-75, 7/75) Carbon-14-methoxy-labeled dichlorvos was incubated *in vitro* with human blood plasma (obtained from a blood bank) under several conditions. Degradation of dichlorvos over time was determined using concentrations of 1.14×10^{-5} M, 1.09×10^{-6} M, 1.08×10^{-8} M and 1.13×10^{-9} M. The curvature of the plots indicated that the disappearance from plasma was not a first-order kinetics reaction. There was a very rapid disappearance within one minute with all four concentrations. Other tests indicated that the degrading enzyme was stable at 37°C and was not inhibited by dichlorvos or its metabolites. Inhibition of plasma cholinesterase under steady state conditions was also measured over several hours with nonlinear results with less inhibition as a function of time. The author considered the cause as perhaps due to the dephosphorylation of the dimethyl phosphorylated enzyme. When infusion of dichlorvos was stopped, a rapid reversal of activity was measured but the reversal was not complete, stopping at about 70% inhibition, representing the amount of monomethyl phosphorylated state of the enzyme, or "aged" enzyme. From the results, the author concluded that it would take 7 to 8 hours to inhibit 5% of the enzyme at steady-state concentration of 1×10^{-9} M dichlorvos. Supplemental study. (Gee, 5/25/99)

[No record number] Boyer, A. C., L. J. Brown, M. B. Slomka and C. H. Hine, 1977. Inhibition of human plasma cholinesterase by ingested dichlorvos: Effect of formulation vehicle. (Shell and University of California, SF, in: Toxicol. Appl. Pharmacol. 41: 389 - 394.) Twenty-four male volunteers, ages 21 - 45 years, were divided into four groups: 1) 0.9 mg dichlorvos 3X daily in a premeal capsule in cottonseed oil; 2) in gelatin salad during meal or 3) placebo group receiving cottonseed oil capsule or 4) gelatin. Average weight was 81 kg with a range of 64 - 106 kg (dose equivalent to 0.01 mg/kg 3X daily). Dosing was carried out over 21 days. Plasma and RBC cholinesterase activities were measured pretest, twice a week during dosing, and for 7 weeks following dosing period. Blood for cholinesterase determinations was collected prior to breakfast. Plasma and RBCs were separated with plasma cholinesterase determined immediately and RBC the following day using a pH stat apparatus. Results: No signs or symptoms were noted. Only plasma cholinesterase was inhibited "to any significant extent". Dichlorvos in cottonseed oil was more effective than in gelatin at inhibiting plasma cholinesterase with gelatin being about 64% as effective. At 21 days, the percent inhibition with gelatin was about 30% and with cottonseed oil, 40%. The half-life of regeneration of plasma cholinesterase was estimated to be 13.7 days. Supplemental study. (Gee, 5/25/99)

[No record number] Cavagna, G., G. Locati and E. C. Vigliani, 1969. Clinical effects of exposure to DDVP (Vapona) insecticide in hospital wards. (University of Milan, Institute of Occupational Health, in: Arch. Environ. Health 19: 112 - 123 (1969)). Healthy adults, adult patients, sick children and women in labor were exposed to DDVP. Blood for cholinesterase determinations was obtained and activity determined by pH titration. The activity of

cholinesterase in all patients/subjects was stated to be normal. Vapona strips were installed at 1 strip/30 m³ (about 1/1000 ft³). Air samples were taken at 1 meter above the floor in several ward locations for the first 15 days after the strips were installed. In addition, 12 babies aged 4 - 12 months of age wore clothes that had been exposed to DDVP. The air concentration in winter reached levels above 0.2 mg/m³ with a maximum of 0.28 mg/m³ fifteen days after installation, then decreasing. In 5 patients exposed for 24 hr/day to 0.1 to 0.28 mg/m³, plasma cholinesterase was decreased to an average of 54% of pre-exposure activity with a range of 35 to 75%. No reduction was seen in RBC activity. In 17 patients exposed for 16 hrs/day at the same levels, neither plasma nor RBC cholinesterase was reduced. At 0.02 to 0.1 mg/m³ for 16 and 24 hours/day, there was no inhibition of cholinesterase. Patients with liver disease showed inhibition of plasma cholinesterase even below 0.1 mg/m³ for 16 hours. No clinical symptoms were reported by these patients. Children showed a similar pattern. The authors concluded that exposure to concentrations of DDVP below 0.1 mg/m³ even for 24 hours/day did not decrease plasma or RBC cholinesterase activity except for plasma in liver diseases. Although the report gives the hours per day for exposure, there are no data on the length of days of exposure for determination of acute effects on plasma cholinesterase, the only parameter showing an effect under the conditions of the study. No individual data. Supplemental study. (Gee, 6/3/99).

[No record number] Cavagna, G., G. Locati and E. C. Vigliani, 1970. Exposure of newborn babies to "Vapona" insecticide. (University of Milan, Institute of Occupational Health, in: Europ. J. Toxicol. 1: 49 - 57 (1970)) Healthy babies born to women exposed during labor and delivery or under 2 different conditions were compared with unexposed babies for blood cholinesterase activity at birth (umbilical cord) and 5 days later. Plasma and erythrocyte activities were measured by pH titration of Jensen-Holm. The activity in babies born to mothers exposed to DDVP (concentrations ranging from 0.095 to 0.25 mg/m³), about 20 minutes 6 times daily, showed no alteration in cholinesterase activity compared with controls. Babies in a well ventilated nursery were exposed to DDVP from 1 strip/40 m³ or in a less well ventilated nursery at 1 strip/30m³ for 5 days. Concentrations under good ventilation ranged from 0.05 to a maximum of 0.125 mg/m³ as estimated from a graph. With less ventilation, the concentration ranged from 0.05 to a maximum of 0.275 mg/m³ (time-weighted concentrations were 0.152 and 0.159 mg/m³ in the two poorly ventilated rooms). No significant effect on plasma or red cell cholinesterase was measured in any group. Limited individual data. The authors concluded that exposure of newborns to Vapona strips at 1/30 m³ did not have an adverse effect under the conditions of the study. Supplemental study. (Gee, 6/3/99)

[No record number] Coulston, F. and T. Griffin, 1977. Cholinesterase activity and neuromuscular function of Rhesus monkeys exposed to DDVP vapors. (Albany Medical College, Draft document, 5/31/77) Male and female rhesus monkeys were exposed to a constant concentration of dichlorvos at 0.051 ug/l for 23 hours per day for three months [estimated at 20 ug/kg/day]. Analytical concentrations of DDVP in the chamber were determined at frequent intervals. Parameters measured included plasma and erythrocyte cholinesterase activity using the method of Ellman et al. Cholinesterase determinations were made pretest and at monthly intervals. Hematology and clinical chemistry parameters included hemoglobin concentration, packed cell volume, total erythrocyte and leucocyte counts, sodium, potassium, creatinine, bilirubin, glucose, total protein, SGPT, SGOT, LDH and inorganic phosphate. Electromyographic studies were performed on lightly anesthetized animals with stimulation of the ulnar nerve and electrodes placed on the tendon and the "belly" of the flexor carpi ulnaris muscle. The intensity of the stimulus was varied. RESULTS: Analytical concentrations ranged from 0.038 to 0.068 ug/l with an average of 0.051 ug/l. No changes in behavior, pharmacologic or toxicologic conditions were noted, including pupillary constriction, muscular

fasciculation, tremors, hyper- or hypo-activity, anorexia, vomiting or stool consistency. No changes in clinical chemistry or hematology parameters were noted. No effect was seen on the electromyographic studies due to exposure to dichlorvos. **CHOLINESTERASE:** Plasma cholinesterase was reduced to 72% of baseline at 3 months ($p < 0.05$) and erythrocyte activity was reduced to 64% of baseline ($p < 0.01$). Individual data were included. Supplemental study. (Gee, 5/26/99)

[No record number] Durham, W. F., T. B. Gaines, R. H. McCauley, Jr., V. A. Sedlak, A. M. Mattson, and W. J. Hayes, Jr., 1957. Studies on the toxicity of O,O-dimethyl-2,2-dichlorovinyl phosphate (DDVP). (Public Health Service, Savannah, GA, in: Am. Med. Assoc. Archives of Ind. Health 15: 340 - 349) Effects of technical DDVP of rats, monkeys, hens and workers were studied by the oral, dermal or inhalation route. **RAT:** Acute oral LD_{50} in males was 80 mg/kg and in females, 56 mg/kg. Dermal LD_{50} was 107 mg/kg in males and 75 mg/kg in females. Subchronic : Groups of 10 female rats were given doses of 0, 5, 20, 50, 200, 500 or 1000 ppm in the diet over a period of 90 days. Plasma and erythrocyte cholinesterase levels were determined periodically (days 3, 11, 30, 60 and 90) using the electrometric method of Michel. At 5 and 20 ppm (0.4 and 1.5 mg/kg), there was transitory depression in plasma but not erythrocyte cholinesterase with recovery by day 30. At 50 (3.5 mg/kg), depression of plasma activity continued through day 60 but recovered by day 90 and RBC activity recovered by day 30. At the higher doses, recovery was not complete by day 90. Inhalation: Walls and ceiling were sprayed with 2.5% DDVP in xylene and rats were exposed for two weeks total with plasma and RBC cholinesterase being determined after one and two weeks. The initial concentration peak value was 6 ug/L with a decrease by the third day to < 1 ug/L. Cholinesterase depression was marginal (5 - 17%). **MONKEYS:** Dermal applications at 50, 75 and 100 mg/kg/day were made for 5 days/week until the animal died. Cholinergic signs were seen after 10 to 20 min. Animals died after 8, 10 and 4 doses. Inhalation: Exposure the same as for rats. Both plasma and erythrocyte cholinesterase were inhibited after 1 week of exposure with a tendency for plasma to recover but little recovery with RBC cholinesterase. **HENS:** Results were reported elsewhere but no signs of paralysis or muscle weakness were noted after subcutaneous doses of 15 mg/kg. **WORKERS:** Five laboratory personnel exposed to "high" but undetermined levels of DDVP for 7 weeks via inhalation and dermal routes were studied for plasma and erythrocyte cholinesterase activity. Plasma levels were not affected but RBC activity was reduced to 68 - 71% of preexposure levels in 4 of 5 men. Supplemental study. (Gee, 5/27/99)

[No record number] Foll, C. V., C. P. Pant and P. E. Lietaert, 1965. A large-scale field trial with dichlorvos as a residual fumigant insecticide in Northern Nigeria. (WHO, in: Bull. World Health Org. 32: 531 - 550) The purpose of the field trial was to determine if either of two types of dispenser would provide sufficient concentration of DDVP to interrupt the malaria cycle. The two types consisted of 1) a solid, impregnated montan-wax strip with not less than 20 g DDVP or 2) a liquid dispenser with 14 g DDVP in 16 ml fluid. The dosage used was one dispenser per 15 m^3 of living space. Subjects were surveyed during the dry season and immediately after rains for parasites in blood samples. Mosquito densities in huts were also surveyed. The failure of dichlorvos to interrupt transmission was believed due primarily to the to the ventilation of the huts and lack of adequate concentration of dichlorvos. There was no discussion of toxic effects to the population. Supplemental study. (Gee, 5/27/99)

[No record number] Funckes, A. J., S. Miller and W. J. Hayes, Jr., 1963. Initial field studies in Upper Volta with dichlorvos residual fumigant as a malaria eradication technique. (CDC, Savannah, GA, in: Bull. World Health Org. 29: 243 - 246) The effect of dichlorvos in a solid dispenser (no details) on the exposed population was determined. Rates of one dispenser per

11 - 28 m³ and one per 1.7 - 2.5 m³ were used. The population consisted of 29 individuals with 17 males and 12 females and an age range of under 6 years to 64 years. Air samples were taken once a week primarily at 6 feet and in the morning and evening. The mean concentration varied with the time of year, being higher in August than in early summer. At one dispenser per 1.7 - 2.5 m³, the range was 0.170 - 0.84 ug/L. The authors found no significant effect of exposure to dichlorvos on cholinesterase (plasma or RBC), hematocrit or hemoglobin levels. Supplemental study. (Gee, 5/27/99)

[No record number] Gratz, N. G., P. Bracha and A. Carmichael, 1963. A village-scale with dichlorvos as a residual fumigant insecticide in Southern Nigeria. (WHO Insecticide Testing Unit and NIH, in: Bull. World Health Org. 29: 251 - 270) Several types of dispensers were used: 1) solid mortan wax impregnated with dichlorvos containing 40 g of technical DDVP; 2) liquid type in a plastic container with 14 g technical DDVP and 3) a solid plastic dispenser with 30% DDVP or flat strips with 20% DDVP. Temperature and humidity were recorded over some months' time. The effectiveness of location within the hut (height) on mosquito control was determined using bioassays with several genus of mosquitos in cages. Placement of the dispensers gave best control when suspended at about 12 feet mid-way between the ridge pole and top of inner partition walls of the hut. Testing in various types of huts was also conducted. The concentration of dichlorvos in the air of huts was measured and found to be influenced by temperature, humidity and ventilation with higher temperature yielding higher concentration and higher humidity a decreased concentration. Also, concentrations at the 2-foot level were 10 - 20% that at the 12-foot level in the hut. Although dichlorvos is heavier than air, ventilation factors influence the concentrations. Plasma and red blood cell cholinesterase was estimated using Michel's micro-method. Activity was compared after 5 and 7 weeks exposure with that in a control village. The authors concluded that there was no significant change in plasma or RBC cholinesterase activity as a result of continual exposure to dichlorvos. Supplemental study. (Gee, 5/26/99)

[No record number] Hass, D. K., J. A. Collins and J. K. Kodama, 1972. Effects of orally administered dichlorvos in rhesus monkeys. (Shell Chemical, in: J. Am. Vet. Med. Assoc. 161: 714 - 719) Rhesus monkeys, either normal or infected with *Schistosoma mansoni*, were given one of several regimens of dichlorvos for 10 to 21 consecutive days. Dichlorvos, 20%, was given orally in a polyvinyl chloride resin pellet in a capsule once or twice daily. Uninfected monkeys, 2 per group, were given 20, 40 or 80 mg/kg b. wt. for 21 days. No deaths occurred but clinical signs included reduced appetite, diarrhea, emesis and salivation, increasing in number of days with dose. No tremors, ataxia, severe salivation or convulsions were noted. Although no data were reported, the text states that cholinesterase inhibition "was virtually complete" after 7 days and remained so up to the 21st day. Cholinesterase data for the infected monkeys, treated at one of several doses for 10 days (once or twice daily) indicated considerable inhibition of both plasma and erythrocyte cholinesterase with recovery toward normal activity being more rapid with plasma when dosing ceased. Erythrocyte activity required about 60 days to recover to pretreatment levels. With twice daily treatment, the pattern was similar to once daily dosing. Other hematological parameters measured in infected animals (including SGOT, SGPT, Alkaline phosphatase, hemoglobin, white blood cell count) were similar to control values. Supplemental study. (Gee, 5/26/99)

[No record number] Hayes, W. J. Jr., 1961. Safety of DDVP for the disinfection of aircraft (Toxicology Section, Public Health Service, Atlanta, GA. In: Bull. World Health Org. 24: 629 - 633). This paper was presented to the WHO Expert Committee on Insecticides and contains no original data. The figure and table are based on Durham et al., 1959 and 1957

respectively. Supplemental reference. (Gee, 5/26/99)

235 - 215 164807 Hunter, C. G., 1969. "Report on initial studies of deliberate exposures to high concentrations of dichlorvos by human subjects." (Shell Research Ltd., Tunstall Laboratory, 1969). Six adult males were exposed to dichlorvos vapor (>98% purity), head and neck. Parameters measured included plasma and erythrocyte cholinesterases, creatinine, phosphate, others. Concentrations ranged from 6.3 to 52 mg/m³ from 20 to 240 minutes. At 18.7 mg/m³, 120 minutes, RBC was inhibited approximately 20% and required over 14 days to recover. At that same exposure, plasma cholinesterase was inhibited 66% with 11 days to recover. The percent depression for plasma cholinesterase was not strictly related to dose or time. No inhibition of red cell cholinesterase was found at 41.5 mg/m³ for 24 min. No visual disturbances were noted. No other parameters were changed. Supplemental study. (Gee, 6/1/99)

235 - 215 164806 Hunter, C. G., 1970. "Dichlorvos: inhalation exposures with human subjects. Part I." (Shell Research Ltd., Tunstall Laboratory, TLGR.0061.70, 1970) Adult male and female volunteers were exposed continuously by total body exposure wearing clothing from 2 to 7 ½ hours. Technical dichlorvos, > 94.6%, was used to generate atmospheres. Target level was 1 mg/m³, the threshold limit value adopted by the Am. Conf. Gov, Ind. Hygienists. Clinical and physiological observations were made including plasma and erythrocyte cholinesterase activity, respiratory activity, EEG, urinalysis and hematology. Cholinesterase was measured pretest, immediately following exposure and after 16 - 18 hours. No effects were noted on parameters other than plasma cholinesterase. Exposures of 400 mg/min/m³ caused decreased plasma cholinesterase compared with pretest levels, being reduced in the range of 20 to 30%. Continuous exposure for 6 - 7 hours were needed to decrease the plasma cholinesterase. Supplemental study. (Gee, 6/1/99)

235 - 215 164806(part 2) Hunter, C. G., 1970. "Dichlorvos: inhalation exposures with human subjects. Part II." (Shell Research Ltd., Tunstall Laboratory, TLGR.0067.70, 1970) Seven adult males were exposed by the head and neck using a "bell jar" to dichlorvos in concentrations ranging from 1 - 53 mg/m³, 1 to 4 hours. Symptoms were confined to irritation of the throat, some rhinorrhea at the highest concentration, and slightly reduced erythrocyte cholinesterase in one subject only at 1,450 mg/min/m³. No visual effects were reported. Plasma cholinesterase was affected by exposure related to the concentration and time of exposure both immediately after exposure and 16 - 20 hours later. One subject had approximately 90% inhibition of plasma cholinesterase immediately after exposure to 5,100 mg/min/m³ with some inhibition still present at day 20 (30% inhibition compared with pretest value). Erythrocyte activity was not affected. Supplemental study. (Gee, 6/1/99).

[No record number] The Kettering Laboratory, 1965. Evaluation of safety in the use of Vapona (R) insecticide resin vaporizers. (University of Cincinnati, OH, 6/65) In part I, 10 volunteers were exposed to Vapona Resin Vaporizers (20% dichlorvos in resin) by either 30 minutes of handling the Vaporizers or by having a portion taped to the skin of the forearm for 30 minutes on 5 consecutive days. Plasma and erythrocyte cholinesterase activities were determined days -1, 3 and 5. There was no inhibition of cholinesterase activity as measured by the method of Michel. In part II, Vaporizers were installed in homes at 1 per 1000 ft³, the recommended rate. For two families, the Vaporizers were changed periodically over 6 months and for 6 families, for two months. Air samples taken from the homes of the first two families indicated a concentration of 0.087 - 0.097 ug/L. The concentration in the other 6 homes was not determined. Plasma and erythrocyte cholinesterase activities were measured over the

course of the study. No inhibition of either cholinesterase was found. Supplemental study. (Gee, 5/27/99)

235 - 213 164803 Leary, J. S., W. R. Keane, C. Fontenot, E. F. Feichtmeir, D. Schultz, B. A. Koos, L. Hirsch, E. M. Lator, C. C. Roan and C. H. Hine, 1974. Safety evaluation in the home of polyvinyl chloride resin strip containing dichlorvos (DDVP). (Shell Chemical Co., in: Arch. Environ. Health 29: 308 - 314 (1974)) Three studies were conducted in Arizona. I. Three families with 5 adults and 12 children, ages 1 - 20 years, were exposed to Vapona strips at 1/1000 ft³ changed every three months for 1 year. The number of strips per home ranged from 7.5 to 18. Blood cholinesterases were determined using the micro-Michel method daily for 3 days prior to installation of the strips, once weekly for first month, every two weeks for two months, then monthly for 9 months. II. Twelve families with 22 adults and 32 children, ages 2 - 19 years, were exposed to Vapona strips at the above rate, 4 to 18 per home. The strips were changed monthly. Plasma and RBC cholinesterases were measured periodically. III. Vapona strips were installed at the same rate as in I and II except there were 1 strip per 500 ft³ in the kitchen and dining areas. The test was conducted in winter with low ventilation. Air and food samples were taken. In addition, all volunteers were given physical exams and clinical profiles were taken. Records were kept of the time spent in each home. Results: In I, there was no difference between the plasma and red cell cholinesterase activities between exposed and control groups. In II, the plasma cholinesterase was slightly depressed (15 - 30%) in the exposed group during the winter. Results with RBCs were "erratic" and therefore, difficult to relate to exposure. In III, plasma activity did not differ significantly between exposed and control groups. The RBC activity, however, was slightly lower in the exposed group. The concentration in the air peaked at 0.12 - 0.13 mg/m³ within several days of installation of the strips and declined to a plateau at 0.08 - 0.09 mg/m³. Doubling the number of strips increased the air concentration to 0.16 mg/m³ several days after installation. The air concentration declined to 0 within 17 days after removal of the strips. In food, the maximum of 0.11 to 0.12 ppm was found day 2 - 16. No effects on health were reported. Supplemental study. (Gee, 6/1/99).

[No record number] Mathis, W., A. St. Cloud, M. Eyraud, S. Miller and J. Hamon, 1963. Initial field studies in Upper Volta with dichlorvos residual fumigant as a malaria eradication technique. (Public Health Service, Savannah, GA, in: Bull. World Health Org. 29: 237 - 241) This was an efficacy study on the mortality of *Aedes aegypti* as function of exposure to dichlorvos during weeks 5 - 12 after installation of dispensers. No mammalian toxicological data although presumably the houses were occupied. Supplemental study. (Gee, 5/26/99).

[No record number] Quarterman, K. D., M. Lotte and H. F. Schoof, 1963. Initial field studies in Upper Volta with dichlorvos residual fumigant as a malaria eradication technique. (Public Health Service, Savannah, GA, in: Bull. World Health Org. 29: 231 - 235) This was an efficacy study on the mortality of mosquitos as function of exposure to dichlorvos for 3 to 5 months after installation of dispensers. No mammalian toxicological data. Supplemental study. (Gee, 5/26/99).

[No record number] Rasmussen, W. A., J. A. Jensen, W. J. Stein and W. J. Hayes, Jr., 1963. Toxicological studies of DDVP for disinfection of aircraft. (Public Health Service, Atlanta, GA, in: Aerospace Medicine 34: 593 - 600) Male volunteers, 15 per group, were exposed to dichlorvos in two phases. Phase I: 0 to 6 doses per night of 30-minute duration over 14 days with a total of 39 exposures ranging from 0.14 to 0.33 ug/L. Phase II: 8 30-minute exposures per night, 4 consecutive nights per week for 3 weeks increased to 10 30-minute exposures per night. For the first 10 weeks, the doses were 0.15 to 0.25 ug/L and increased to 0.40 to 0.55 ug/L, 10

doses per night, 4 days per week for 2 weeks. Parameters measured included plasma and erythrocyte cholinesterase activity, reaction time, a number of visual properties, and physical exams. RESULTS: Phase I: No difference in cholinesterase activity between control and exposed groups. Phase II: No effect was found on erythrocyte cholinesterase but plasma cholinesterase was depressed in the exposed group, occasionally reaching statistical significance. When the dose was increased, the plasma cholinesterase was further depressed but once exposure was discontinued, the activity returned to control level in 2.5 weeks. No significant changes in other parameters measured were reported as due to exposure to dichlorvos. The conclusion was that exposure to 0.15 to 0.25 ug/L caused no measurable changes in plasma or RBC cholinesterase activity, vision, airway resistance or reaction time. Supplemental study. (Gee, 5/27/99)

[No record number] Rider, J. A., 1967. Determination of the minimal incipient toxicity of dichlorvos in humans. (Shell Chemical Company, by Gastrointestinal Research Laboratory, Franklin Hospital, San Francisco, 10/67) Male volunteers were given total doses of 1.0, 1.5, 2.0 or 2.5 mg/day in capsules, with one capsule given at 8 a.m. and one at 3 p.m. for 28 days. Further testing was done at 1.5 mg/day for 60 days followed by cholinesterase measurement for 74 days. Both plasma and erythrocyte cholinesterase activity were determined using the method of Michel. There were no significant effects on cholinesterase at 1.0 mg/day. At 1.5 mg/day [estimated as 0.02 mg/kg/day assuming 70 kg body weight], there was a maximum decrease of 15% in plasma cholinesterase the second day after cessation of dosing with no effect on RBC cholinesterase. At 2.0 mg/day, plasma cholinesterase was depressed beginning the second week of dosing with a maximum of 29% the second day after dosing ceased with no effect on RBC cholinesterase. At 2.5 mg/day [0.04 mg/kg/day], plasma cholinesterase was depressed during the second week with dosing stopped when it reached 30% depression after 20 days. The activity recovered to 99% of control in 15 days. With prolonged dosing at 1.5 mg/day for 60 days, the dose being selected as just below the level of minimal incipient toxicity, plasma cholinesterase was depressed during the second week of dosing and continued during the 60-day period reaching a maximum of 41%. Controls also showed some depression in plasma cholinesterase during the second half of the dosing period so that when the activity of the dichlorvos- treated group was adjusted, the maximum decrease was 27%. Following cessation of dosing, the plasma cholinesterase activity returned to within the range of pre-dosing levels within 2 weeks. Erythrocyte activity showed little effect with any of the exposure regimens. Using a criterion of 20 to 25% depression in plasma or erythrocyte cholinesterase activity as "minimal incipient toxicity", 1.5 mg/day [0.02 mg/kg/day] would be just below the dose of dichlorvos giving that effect. Supplemental study. (Gee, 5/27/99)

[No record number.] " Effects of dichlorvos (DDVP) inhalation on the activity of acetylcholinesterase in the bronchial tissue of rats" (Schmidt, G., M. Schmidt, M. Nenner and F. Vetterlein, Institut fur Pharmakologie und Toxikologie der Universitat Gottingen, FRG), published in: *Arch. Toxicol.* 42: 191 - 198 (1979), Male Sprague-Dawley rats (180 - 220 g) were exposed to DDVP from Vapona strips for 3, 7 or 14 days. The DDVP atmosphere was generated by cutting commercial strips into equal portions of 1:1, 1:2, 1:4, 1:8, 1:16, 1:32 or 1:64. Measured concentrations ranged from 0.83 to 56.64 ug/l in air as determined by the degree of inhibition of acetylcholinesterase from bovine erythrocytes compared with known concentrations of DDVP. At the end of the exposure period, rats were sacrificed and bronchial tissue isolated. The acetylcholinesterase activity of homogenates of bronchial tissue and of erythrocytes was determined with acetylcholine iodide. Histochemical detection of acetylcholinesterase was based on the thiolacetic acid method with the liberation of hydrogen sulfide and PbS precipitate formation in tissue. The reported NOEL for ACHE inhibition in bronchial homogenate was 0.2

ug/l, the reported concentration of DDVP from Vapona strip in a normally ventilated room. At 0.82 and 1.8 ug/l, the AChE was inhibited to 63 and 52% of control. The NOEL for erythrocyte inhibition was 1.8 ug/l. No animals exposed to DDVP showed histochemical reaction indicating enzyme activity. Therefore, the NOEL for that assay was less than 0.2 ug/l. No clinical signs or pulmonary function data were included in the report. The toxicological significance of the findings could not be evaluated. The authors discussed the results in terms of a possible role in pathological conditions. **Supplemental study.** (Gee, 11/8/99)

[No record number] Slomka, M. B. and C. H. Hine, 1981. Clinical pharmacology of dichlorvos. (Shell, published in: Acta pharmacol. et toxicol. 4 (suppl. V): 105 - 108) Purified dichlorvos (97%) was incorporated into polyvinyl chloride resin pellets which were encapsulated into gelatin capsules for dose administration. Male volunteers were given either a single dose, dosing for 7 days or dosing with an increasing dosage regimen each week with a maximum of two increases. Plasma and RBC cholinesterase activities were measured by the potentiometric titration method of Michel with the maximum depression at 24 hours or 48 hours after treatment reported. Single dose: 0, 0.1-1, 2-3, 4-6, 7-9, 10-12, 13-16, 17-20, 21-26 and 32 mg/kg dichlorvos. There were varying numbers of subjects per group. Both plasma and RBC cholinesterase activities were depressed in a dose-related manner. Plasma cholinesterase was more affected than RBC with a maximum depression of approximately 80% at 6 mg/kg, expressed as percent of pretreatment values. Less than 50% depression of RBC cholinesterase activity was found at 4 times that dose. Multiple doses: 0, 1, 2, 4, 8, 16 and 32 mg/kg for 7 days oral dosing except at 8 and 32 mg/kg which were of shorter duration due to cholinesterase depression. At 1 mg/kg, plasma was depressed 65 - 80%, RBC depressed 5 - 30%. At 2 mg/kg, plasma was depressed 75 - 85% and RBC, 25 - 45%. Side effects were reported in all groups including controls and involved the gastrointestinal tract or central nervous system. No data but there was a statement that no changes were noted in clinical or other laboratory examinations. **Supplemental study.** (Gee, 5/27/99)

[No record number] Stein, W. J., S. Miller and L. E. Fetzer, Jr., 1966. Studies with dichlorvos residual fumigant as a malaria eradication technique in Haiti. III. Toxicological studies. (Public Health Service, in: Am. J. Tropical Med. Hyg. 15: 672 - 675) Three groups of workers were studied: 1) twelve applicators who removed and installed new dispensers in houses, 2) two supervisors and 3) four laborers who changed the old for new dispensers. A medical history, physical examination and plasma and erythrocyte cholinesterase activities were obtained. The workers were observed for as long as three weeks with cholinesterase determined twice a week for applicators and three times per week for laborers. Air samples were taken in the shed used by the laborers at several locations during the study. There was no affect on RBC cholinesterase in any group. Plasma cholinesterase was depressed in both the applicators (still within normal limits after 2.5 weeks of exposure) and laborers (greater depression than applicators with the maximum depression reached in about a week with no further change in the final two weeks of observation. Data were presented graphically as the mean cholinesterase activity (? pH/hr) over the test period. The concentration of dichlorvos in the air of the shed varied with location and activity, being as high as 2.13 ug/L in the center of the work area at the end of a workday. On the following day, concentrations ranged from 0.29 to 1.18 ug/L, depending on location of the sampling. No illnesses were attributed to dichlorvos exposure. Because of the variation in the air samples, an accurate determination of worker exposure was not feasible. **Supplemental study.** (Gee, 5/27/99)

235-217 165876 Stevenson, D. E. And D. Blair, 1969. "A preliminary report on the

inhalation toxicity of high concentrations of dichlorvos.” (Shell Research Limited, Tunstall Laboratory, London, TLGR.0024.69, Project 507521, 5/27/69) Rats (CFE), mice (CF No. 1) and guinea pigs were exposed to DDVP and dichloroacetaldehyde (DCA) by inhalation. DCA is a hydrolysis product of DDVP. The concentration of DDVP in the chamber air was analyzed by gas chromatography. DCA was determined by a colorimetric method. A series of 10 experiments were conducted with exposure lasting 6 - 7 hours and the number of exposures ranging from 1 to 5. In the first four experiments with mice and rats, the authors state that the results were inconsistent in terms of mortality, the only specific endpoint given in Table 1. Doses were 40 to 80 ug/l DDVP with DCA content undetermined in experiments 1 - 3. For example, in Expt. 1, 0/8 mice died, but had signs of toxicity(not described), at 80 ug/l, 5 exposures of 6 - 7 hours. In expt. 2, 1/8 mice died after 4 exposures at 40 ug/l. In expt. 3, 16/16 mice died at 50 - 80 ug/l, 4 exposures. The remark column contains the statement “1-2 days” without explanation as to the meaning. In experiment 4, 8/8 mice died at 80 ug/l after a single exposure. The authors concluded that the length of time the apparatus was in use and possibly the relative humidity, which could influence the hydrolysis to DCA, caused the variability in results. Relative humidity was given as 20 - 30% in expts. 1 - 4. Death in animals was stated to be preceded by clinical signs (including tremors, salivation/lachrymation, muscle paralysis, prostration). Rats under the same conditions were less susceptible to mortality. Guinea pigs were even less affected in expt. 1, the only one in which they were included. In experiments 5 - 10, the DCA content was monitored and the relative humidity controlled. In mice at 80 - 134 ug/l DDVP(expts. 5 and 6), there was mortality, although not 100%, being 4/12 females and 31/128, both sexes. At 41 to 80 ug/l (length of exposure to any given concentration not stated), no mortality occurred in mice receiving 4 or 5 exposures. The text states there were no clinical symptoms. The reason for the seemingly sharp difference in mortality with mice around 80 ug/l was not addressed. No mortality occurred in male or female mice exposed to 70, 135 or 130 ug/l DCA in a single exposure of 7 hours. Guinea pigs suffered no reported effects at 90 - 122 ug/l in 4 exposures of 7 hours. Rats showed an intermediate response. The authors concluded that the “no-visual-effect” levels were 130 ug/l for guinea pigs and 50 ug/l for rats and mice. Cholinesterase activity was not determined. The authors speculated that there would be inhibition of brain and blood cholinesterase activity but gave no data or citation. Inhaled doses were calculated by the authors to be 0.22, 0.61 and 0.72 l/kg min for guinea pig, rat and mouse, respectively, at the same atmospheric concentration of DDVP [not stated]. If the retention fraction were the same for all three species, then the mouse was stated as receiving over 3 times the dose of the guinea pig. Deficiencies in the report include a range of concentrations over time rather than a single concentration so that actual exposure cannot be determined, no individual data for animal responses/mortality (the only endpoint quantitated), no clinical chemistry for cholinesterase inhibition. Because of these deficiencies, this report cannot be used to determine a NOEL for acute effects. The report does suggest that the order of increasing sensitivity was guinea pig, rat, mouse under the conditions of the study. Supplemental study. (Gee, 6/16/99)

[No record number] Stevenson, D. E. and D. Blair, 1977. The uptake of dichlorvos during long-term inhalation studies. (Shell Research Ltd., Tunstall Laboratory, in: Proc. Eur. Soc. Toxicol. 18: 215 - 217) A general discussion of methods which could be used to determine uptake of dichlorvos by routes other than inhalation during an inhalation study. No data. (Gee, 5/27/99)

235 - 214 164804 Thorpe, E., A. B. Wilson, K. M. Dix and D. Blair, 1972 “Teratological studies with dichlorvos vapour in rabbits and rats” (Shell Research Ltd., Tunstall Laboratory, in: Arch. Toxikol. 30: 29 - 38 (1972)) This is a publication of the studies reviewed in 235-072,

Record numbers 035427 (rabbit) and 035428 (rat) in 1985. Neither study was found acceptable. In brief: Rats and rabbits were exposed to Dichlorvos technical (>97%) by inhalation at nominal doses of 0, 0.25, 1.25 and 0.625 ug/L of air. Carworth Farm E strain of rats were exposed from day 1 to day 20 of pregnancy, 15 / dose group, for 23 hours daily, 7 days per week. Dutch rabbits, 20/group, were exposed as above from day 1 to 28 of gestation. Fetuses were examined externally and approximately half were given visceral exams and half, skeletal exams. Plasma, erythrocyte and brain cholinesterase was determined from "a selection of the adult females". A second study with rabbits was performed at 0, 2 and 4 ug/L due to significant losses at 6.25 ug/L. **RESULTS:** Rats: at the lower two doses, no observations were made but at the high dose, 6.25 ug/L, they appeared "less active". At 0.25 ug/L, no significant cholinesterase inhibition was found (plasma = 97% and RBC = 105% with brain 98% compared with controls). At 1.25 ug/L, plasma was 67% of control, RBC was 71% and brain, 72%; at 6.25 ug/L, plasma was 27%, RBC was 12% and brain was 17% of control. NOEL = 0.25 ug/L. There was no effect on fetal resorption, late fetal death, litter size or fetal weight. Rabbits: 16 or 20 at 6.25 ug/L died or were terminated because of toxicity with 9 of the losses occurring within 7 days of the chamber concentration reaching 8 ug/L [presumably in error]. In the second experiment, 6 rabbits at 4 ug/L died or were killed because of toxicity, again due to a spike in the concentration of dichlorvos above the nominal level. At 0.25 ug/L, plasma cholinesterase activity was 85%, RBC was 86% and brain was 90% of control values. At 1.25 ug/L, plasma activity was 65% of control, RBC was 32% and brain, 44%. At 6.25 ug/L, no data were recorded due to toxicity. NOEL = 0.25 ug/L. In rabbits, there were no effects at 0.25 or 1.25 ug/L but there was a slight depression in fetal weight at 4 ug/L (20.2 g versus 23.1 g in control). **CONCLUSION:** There was no evidence of a teratogenic effect with exposure to dichlorvos under the conditions of the study in either rat or rabbit. **NOTE:** The authors calculated that the low concentration of 0.25 ug/L, based on respiratory properties, would be 110 ug/kg in the rabbit and 300 ug/kg in the rat over 24 hours. This was compared with 6 ug/kg for humans (no details). Supplemental study. (Gee, 5/28/99)

235 - 042 911129 Tracy, R. L., J. G. Woodcock and S. Chodroff, 1960. "Toxicological aspects of 2,2-dichlorovinyl dimethyl phosphate (DDVP) in cows, horses, and white rats." (Norda Essential Oil and Chemical Co., in: J. Econ. Entomol. 53: 593 - 601 (1960)) Horses: Five horses were exposed in a stable to dichlorvos at concentrations varying from 0.24 to 1.48 ug/L of air for 22 days. The dichlorvos was sprinkled daily onto a concrete walkway between the rows of stall and the 4 ventilators and 2 windows were open. Erythrocyte cholinesterase activity was depressed early in the exposure but appeared to recover by day 11. Plasma cholinesterase was unaffected by exposure compared with control level in unexposed horses. Cows: Two cows with suckling calves were fed DDVP in increasing doses beginning at 0 ppm and increasing to 3000 ppm (27 mg/kg). No significant depression of RBC cholinesterase activity was found up to 200 ppm (1.8 mg/kg) in the cows or the suckling calves. At 500 ppm (4.5 mg/kg) RBC activity was significantly depressed in the cows but not the calves. Further increase in doses did not further depress the RBC activity in the cows. Assay of plasma activity varied markedly and was thought unreliable. At the highest dose tested for 1 day, 3000 ppm (27 mg/kg), the single cow collapsed but recovered. Plasma assay of the milk, urine and feces of the cows using *M. domestica* (house flies) did not produce kills. Rats: Seven rats with litters 1 - 12 days of age were given DDVP by gavage at 0, 10, 20, 30 or 40 mg/kg with increasing doses per female. Doses up to 20 mg/kg in dam did not cause symptoms although RBC cholinesterase was depressed nearly 50%. At 30 mg/kg, animals exhibited shock symptoms with recovery. At 30 and 40 mg/kg, erythrocyte cholinesterase was severely inhibited but plasma activity were not. The weight gain of the litters was near controls. The plasma and RBC cholinesterase activities in the litters were within normal range. Tissue studies: Several tissues

(liver, brain, muscle and small intestine) were assayed with *M. domestica* for the ability to inactivate DDVP. The liver appeared to be the organ for detoxification. Supplemental study. (Gee, 5/28/99)

[No record number] Uchiyama, M., T. Kawakami and H. Hiuga, 1967. Effect of Vapona/strips to human beings and the method of determination of DDVP concentration in the air. (Tohoku Univ., Japan, 11/67) Pediatric patients were exposed in a ward at 3 strips Vapona per 93 m³. Serum cholinesterase and liver function were determined over approximately 90 days. There was no effect on cholinesterase. Twenty adult patients were exposed to Vapona strips at 4/120 m³ for 72 days. No effect due to the DDVP was noted. Cholinesterase was determined using a colorimetric assay based on Hestrin's procedure with the results based on index figures from 42 healthy persons as 100. Although an analytical method for determining DDVP in air was described, the concentrations in the air of the wards over time was not presented. Mice: Groups of ten mice were exposed to DDVP at 10 and 100 times the "standard" dosage in inhalation chambers. Standard was defined as 1 strip/28 m³. Plasma, erythrocyte and brain cholinesterase activities were determined over a period of 3 weeks. The control group = 100%. At the standard exposure rate (0.46 to 0.2 ug/L), no cholinesterase inhibition occurred. At 10X (DDVP at 1.54 to 1.7 ug/L), no inhibition of plasma activity occurred but RBC was 94.5% of control after 2 weeks and brain was approximately 93% of control after 2 or 3 weeks. At 100X (DDVP at 12.5 - 14.5 ug/L), plasma was 75% of control at week 3, RBC was 83.8% at 2 weeks and brain was 28.3, 21.4 and 37.0 at weeks 1, 2 and 3 respectively. Supplemental study. (Gee, 5/28/99)

[No record number] Ueda, K. and M. Nishimura, 1967. Effect of Vapona/strips to human beings. (Tokyo Dental College, unpublished data, 1967) In part one, 47 hospital patients were exposed to DDVP at 1 strip/22 m³, stated to be the standard dose. There was no evidence of inhibition of plasma or erythrocyte cholinesterase measured by Michel method. In part 2, two male subjects were exposed either to doses at 5 or 10 times the usual rate, or 10 strips/51.5 m³ and 17 strips/46.8 m³. At 5 times, the air concentrations varied from 2.2 ug/L at 3 hours to 0.8 by 48 hours. At 17 times, the air concentration varied from 8.5 ug/L in the first 12 hours to 2.4 ug/L by 48 hours. At 8.5 ug/L after 12 hours of exposure, [the dose was estimated to be 533 ug/kg/day] the plasma cholinesterase was inhibited by 15 and 24%. In these same individuals, at 4.4 ug/L, 24 hours, [dose estimated at 477 ug/kg/day], plasma cholinesterase was inhibited 33 and 28%. Changes in erythrocyte activity was less than in plasma. The plasma activity recovered by 7 days after exposure discontinued. At the 5 times exposure, no significant inhibition occurred. Supplemental study. (Gee, 5/28/99)

[No record number] Vigliani, E. C., 1971. Exposure of newborn babies to Vapona® insecticide. (Institute of Occupational Health, Milan, Italy, in: Toxicol. Appl. Pharmacol. 19: 379-380 (1971), abstract.) Healthy babies, 22 per group, were exposed for the first 5 days of life in rooms with 1) 1 Vapona® strip/40 m³, 18 hours/day or 2) 1 strip/30 m³ but poorly ventilated. The time-weighted average in 1) was 0.05 mg/m³ and in 2) 0.152 and 0.159 mg/m³. Plasma and red blood cell cholinesterase was determined at birth and at the end of the exposure. The abstract states that there was no effect on either. No data. Supplemental data. (Gee, 5/28/99)

[No record number] Walker, A. I. T., D. Blair, E. D. Stevenson and P. L. Chambers, 1972. An inhalation toxicity study with dichlorvos. (Shell Research Ltd. Tunstall Laboratory, in: Arch. Toxikol. 30: 1-7) The effect of dichlorvos, 20% in polyvinyl chloride strips with either of two plasticizers, was measured in dogs, rabbits and cats with emphasis on

electroencephalographic (EEG) patterns as an indication of central nervous system activity. Formulation A plasticizer was expected to give twice the concentration of formulation B; however, both were similar under test conditions. With group 1, strip A, one strip was located per 1200 ft³ for 8 weeks with no change. With group 2, strip B, one strip was located per 1200 ft³ for 6 weeks and replaced weekly thereafter with strip A. The air concentration with strip A ranged from a high of 0.2 ug/L after installation, reached 0.1 ug/L in a few days and decreased to 0.05 ug/L over 50 days. With B strips, the high was close to 0.3 ug/L and took 30 to 35 days to reach 0.05 ug/L from 0.1 ug/L with an increase each time the strip was replaced. A limited number of animals per species and group were used due to implantation of the electrodes. Two male dogs and rabbits served as controls with 4 or 5 of both sexes exposed to group A strips and 2 or 3 to strip B. The number of cats was even more limited. The relationship of pre- and post-exposure activities for plasma and erythrocyte cholinesterases was determined, using a modified method from Michel. The conclusion was that neither exposure produced any treatment effect. No changes were seen in the EEG recordings. The authors concluded that at concentrations higher than those achieved with normal DDVP strip use, no effects on general health, behavior, cholinesterase activity or EEG patterns were found in dogs, rabbits and cats. Supplemental study. (Gee, 5/28/99)

[No record number] Witter, R. F., T. B. Gaines, J. G. Short, V. A. Sedlak and D. R. Maddock, 1961. Studies on the safety of DDVP for the disinfection of commercial aircraft. (Public Health Service, Savannah, GA, in: Bull. World Health Org. 24: 635 - 642) Seven men and 8 Rhesus monkeys were used in the study. Exposure regimens were designed to simulate disinsection of aircraft. Measurements included plasma and erythrocyte cholinesterase activities by the method of Michel and examination of the eyes for miosis. In the first exposure, the men were exposed for one or two hours on four consecutive days to a range of 0.26 - 0.88 ug/L (mean of 0.48 ug/L). In the second, they were exposed to a range of 0.09 to 3.5 ug/L (mean of 2.1 ug/L) for a total of 4 or 8 hours. Postexposure blood samples were taken up to 7 days. At the lower range of exposure, there was no effect on cholinesterase. At the higher range, there was a "slight" decrease in plasma activity in 2 of 3 men exposed a total of 8 hours (data presented graphically only). No change was noted in RBC activity or in those exposed for 4 hours total. No miosis was found. The monkeys were divided into 4 groups and exposed for 2 hours on 4 consecutive days. Four ranges were used: 0.32 - 0.66 (mean of 0.48 ug/L), 1.2 - 3.2 (mean of 2.3 ug/L), 1.9 - 3.3 (mean of 2.6 ug/L) and 7.5 - 17.9 (mean of 12.9 ug/L). In the first three groups, results were stated to be negative or questionable for plasma cholinesterase. At the highest range, both monkeys had miosis which disappeared, a significant drop in red blood cell and plasma cholinesterase which lasted several weeks after testing was discontinued. The authors concluded that the threshold range for man was 0.09 to 3.5 ug/L compared to an effective concentration for insects of 0.15 to 0.25 ug/L DDVP. Supplemental study. (Gee, 5/28/99)